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COMMUNICATION

Stereoselective synthesis of *N*-aryl proline amides by biotransformation–Ugi-Smiles sequence†‡

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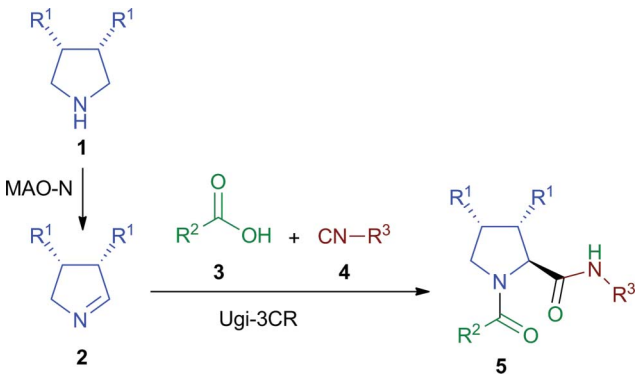
An efficient combination of MAO-N-catalyzed desymmetrization of cyclic *meso*-amines with Ugi-Smiles multicomponent chemistry produced optically pure *N*-aryl proline amides. This method represents the first report of a fully asymmetric Ugi-Smiles process.

The synthesis of complex and challenging target molecules requires sophisticated synthetic concepts and methodologies. Owing to their high flexibility, selectivity, and convergence, multicomponent reactions (MCRs)[1] have emerged as powerful tools in the synthesis of complex, biologically relevant molecules.[2] Undoubtedly the most widely used MCR is the Ugi four-component reaction (U-4CR). This reaction between amines, aldehydes, carboxylic acids and isocyanides affords a wide range of peptidic and peptidomimetic products. However, no catalytic asymmetric version of the U-4CR has been described to date and, as many MCRs, it typically suffers from very poor diastereoselectivity.[3] Recently, we developed a highly stereoselective synthesis of substituted prolyl peptides **5** by combining the biocatalytic desymmetrization of 3,4-*cis*-substituted *meso*-pyrrolidines **1** using an engineered monoamine oxidase N (MAO-N) from *Aspergillus niger*[4] and an Ugi-type three-component reaction (MAO-N oxidation–MCR sequence, Scheme 1).[5] These prolyl peptides are of considerable interest in organocatalysis. This method has also proven very efficient in the synthesis of alkaloid-type compounds[6] and the hepatitis C drug Telaprevir© (Incivek™).[7]

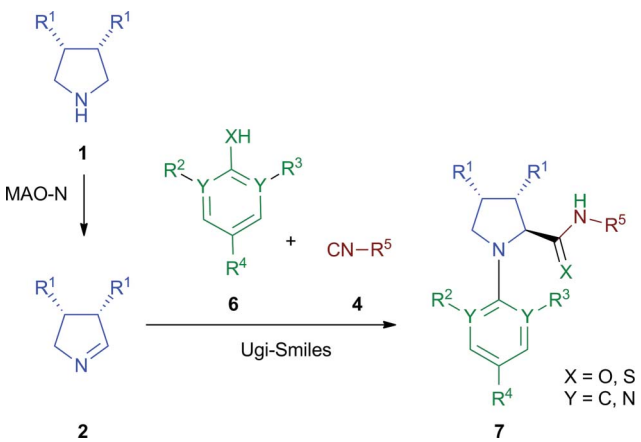
We then decided to investigate the possibility of extending this methodology to other MCRs. The Ugi-Smiles reaction, a variation



Scheme 1 Asymmetric synthesis of prolyl peptides by MAO-N oxidation and Ugi-type 3CR.[5]

of the Ugi reaction in which the carboxylic acid component is substituted by an electron-deficient phenol derivative (or a heteroaromatic analog),[8] is a promising candidate for combination with our biocatalytic oxidation due to its mechanistic similarity with the Ugi reaction. Recently, El Kaïm and coworkers described a three-component Ugi-Smiles coupling of five- and six-membered (racemic) cyclic imines.[9]

Because the optically active 1-pyrrolines generated by MAO-N oxidation are versatile building blocks for a diverse set of MCRs, we envisioned that combining these substituted 1-pyrrolines



Scheme 2 Asymmetric synthesis of *N*-aryl proline amides by MAO-N oxidation and Ugi-Smiles 3CR.

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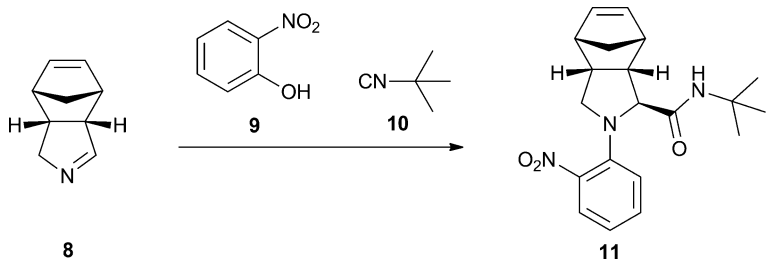
‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. CCDC reference number 844264. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06699d

Table 1 Optimization of the Ugi-Smiles 3CR of bridged imine **8**, 2-nitrophenol (**9**) and *tert*-butyl isocyanide (**10**)



Entry	Solvent	T/°C	Reaction Time	Additives	**8**) : **9** : **10**[a]	Yield (%)
1	MeOH	60	24 h	—	1.0 : 1.3 : 1.3	53[b]
2	Toluene	80	24 h	—	1.0 : 1.3 : 1.3	26[b]
3	MeOH	60	48 h	—	1.0 : 1.3 : 1.3	55[b]
4	Toluene	80	48 h	—	1.0 : 1.3 : 1.3	25[b]
5	MeOH	RT	72 h	—	1.0 : 1.3 : 1.3	39[b]
6	MeOH	40	24 h	—	1.0 : 1.3 : 1.3	43[b]
7	MeOH	125	30 min[d]	—	1.0 : 1.3 : 1.3	40[c]
8	MeOH	150	30 min[d]	—	1.0 : 1.3 : 1.3	40[c]
9	TFE	135	30 min[d]	—	1.0 : 1.3 : 1.3	<10[c]
10	MeOH	RT	24 h	$Sc(OTf)_3$	1.0 : 1.3 : 1.3	34[b]
11	MeOH	60	24 h	$Sc(OTf)_3$	1.0 : 1.3 : 1.3	24[b]
12	MeOH	RT	24 h		2.0 : 1.3 : 1.5	33[b]
13	MeOH	40	24 h	—	2.0 : 1.0 : 1.5	73[b]
14	MeOH	60	24 h	—	2.0 : 1.0 : 1.5	44[b]

[a] Molar ratios of the reactants; [b] Isolated yield; [c] Yield estimated by HPLC analysis; [d] Microwave irradiation in closed vessel; TFE = 2,2,2-trifluoroethanol.

with the Ugi-Smiles MCR would generate highly functionalized, optically pure 3,4-substituted *N*-aryl proline amides (Scheme 2). Similar compounds have been reported to be potent VLA-4 antagonists.[10] These antagonists may be useful in the treatment of diseases like asthma, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis.[11]

We started our investigation by finding the most suitable conditions for the Ugi-Smiles MCR. The reaction of bridged imine **8**, 2-nitrophenol (**9**) and *tert*-butyl isocyanide (**10**) was designated as a benchmark reaction (Table 1). We began by using the conditions reported by El Kaïm *et al.*[12] Unfortunately, these conditions afforded **11** in moderate yield at best (entries 1 and 2, Table 1). Therefore, we opted to extend the reaction time and raise the temperature. However, this did not have any effect and the isolated yield remained more or less the same (entries 3–6, Table 1). Neither microwave irradiation of the reaction mixture (entries 7–9, Table 1) nor the use of $Sc(OTf)_3$ as Lewis acid additive (entries 10 and 11, Table 1) led to an improved yield. In a final attempt to improve the yield we used a two-fold excess of the imine. Performing the reaction at room temperature afforded the product in low yield (entry 12, Table 1). To our delight the yield increased to a satisfactory 73% when the temperature was raised

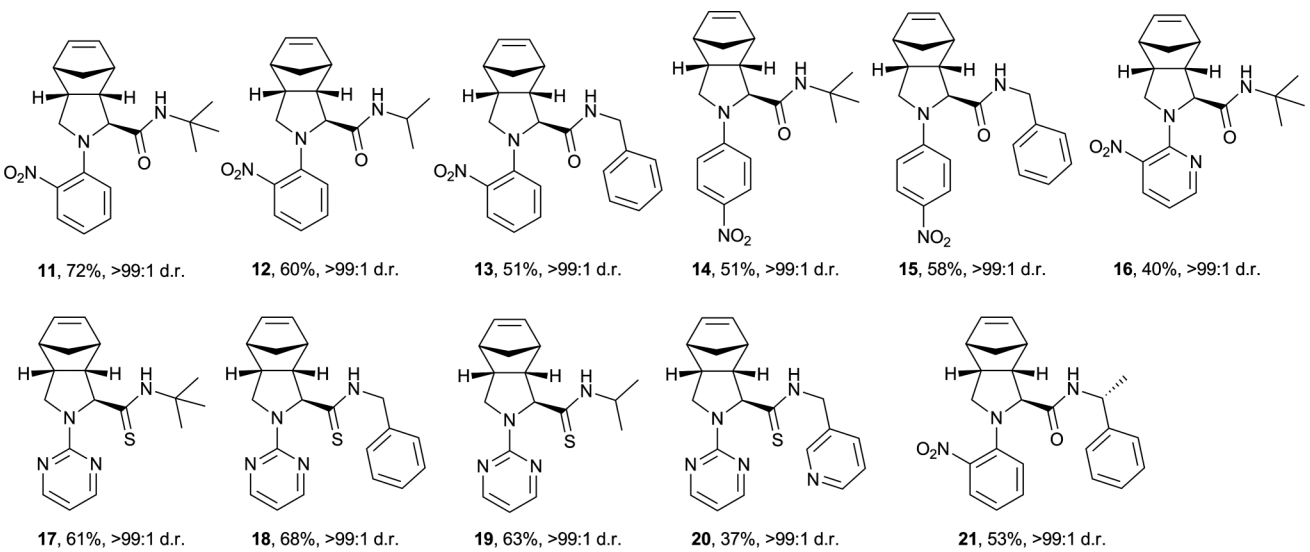


Fig. 1 Scope of Ugi-Smiles 3CR using optically pure **8**. *Reagents and conditions*: imine **8** (2.0 equiv.), (hetero)aromatic alcohol (1.0 equiv.), isocyanide (1.5 equiv.), MeOH, 40 °C, 24 h.

to 40 °C (entry 13, Table 1). Further raising the temperature to 60 °C led to a significant drop in yield, probably due to stability issues of the imine (entry 14, Table 1).[13]

With this procedure in hand we turned our attention to the synthesis of a small set of Ugi-Smiles products. Starting from bridged imine **8**, various phenols and isocyanides were employed to generate the corresponding Ugi-Smiles products **11–21** (Fig.1).

Using *ortho*-nitrophenol and *para*-nitrophenol with different isocyanides gave the desired Ugi-Smiles products in moderate to good yields as single diastereomers (**11–15**, Fig. 1). 3-Nitro-2-pyridinol and 2-mercaptopyrimidine were tolerated as inputs and gave the desired products in moderate to good yields as single diastereomers (**16–19**, Fig. 1).

2-Pyridylmethyl isocyanide was also tolerated as the isocyanide input, affording the corresponding Ugi-Smiles product **20** in fair yield (Fig. 1). In addition, the use of an optically pure chiral isocyanide input [(*R*)-α-methyl-benzyl isocyanide] led to the formation of a single diastereomer with a 2,3-*trans* configuration, confirming that the starting chiral imine is responsible for the diastereoselectivity of the reaction (**21**, Fig. 1). X-Ray crystallographic analysis of **11** (see Fig. 2)‡ unequivocally established the absolute configuration at C2 as (*S*) since the absolute stereochemistry at C3 and C4 positions, resulting from the biotransformation, has been reported previously.[4] Next, the sterically less demanding enantiomerically enriched (1*S*,4*R*)-3-azabicyclo[3.3.0]oct-2-ene (**32**)[4] was used in a series of Ugi-Smiles 3CRs (**22–31**, Fig. 3). Very good diastereomeric ratios were obtained for compounds **22–31** and considerably higher yields were observed compared to reactions using the bulky bridged imine **8** as an input (*cf.* Fig. 2). This observation can be rationalized by steric considerations or by the difference in stability between the cyclic imines used.[13]

Subsequently, we synthesized a set of Ugi-Smiles products (Fig. 4) that can undergo additional complexity-generating reactions, *e.g.* olefin metathesis,[14] cycloaddition reactions (Diels–Alder[15] or azide–alkyne cycloaddition[16]) or Pd-catalyzed cross-coupling reactions[17,18] to provide rapid access to highly complex scaffolds with pharmaceutically interesting properties.

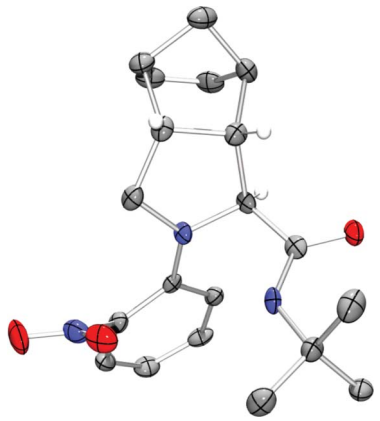


Fig. 2 Single-crystal structure of **11**. Displacement ellipsoids are drawn at the 50% probability level. Most hydrogen atoms are omitted for clarity.

We chose to introduce an azide and allyl functionality into our Ugi-Smiles products by using 2-azidoethyl isocyanide[19] and commercially available allyl isocyanide as an input. The presence of the azide or allyl functionality in the final adduct allows interesting applications to heterocycle synthesis. The desired azide compound **33** was obtained in good yield and diastereoselectivity (72%, d.r. = 88 : 12). Next, we secured Ugi-Smiles adducts **34** (55%, d.r. = 89 : 11) and **35** (34%, d.r. >99 : 1) with the desired allyl functionality. In the latter case, we used the saturated bridged imine **36**[4] as the double bond in **8** could possibly interfere in subsequent follow-up reactions.

Remarkably, Ugi-Smiles products derived from 2-nitrophenol or 3-nitro-2-pyridinol as inputs showed unusually high α_D values (see the ESI‡). For example, compound **11** has a specific rotation of −1043.1°, the highest specific rotation ever reported for a

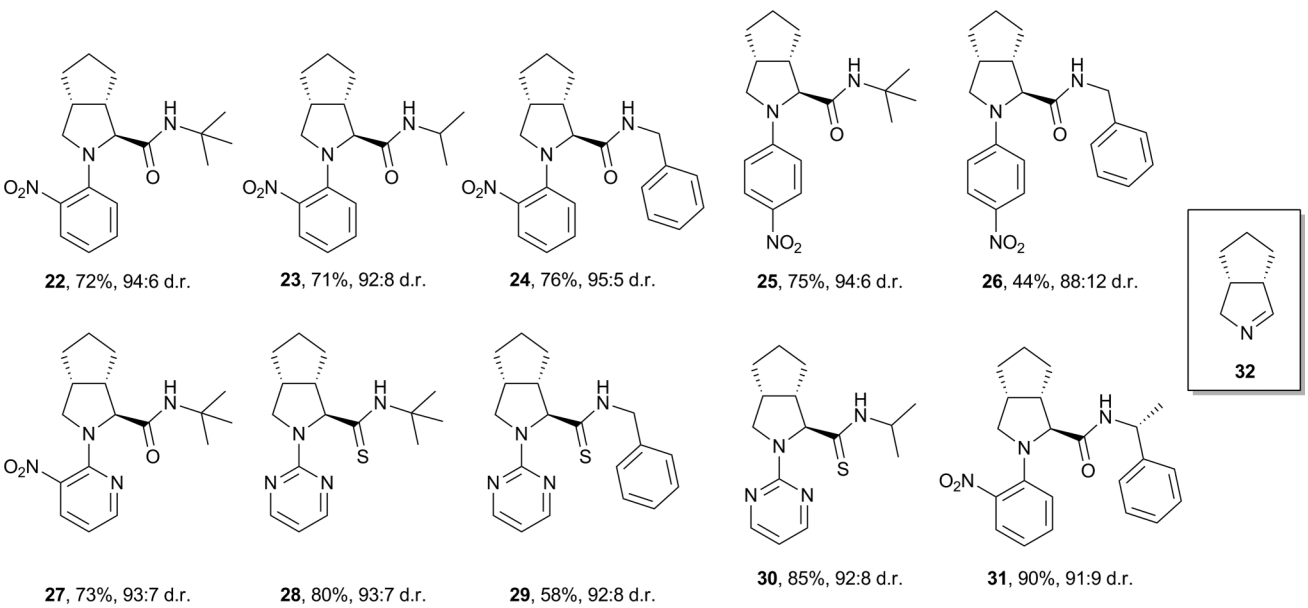
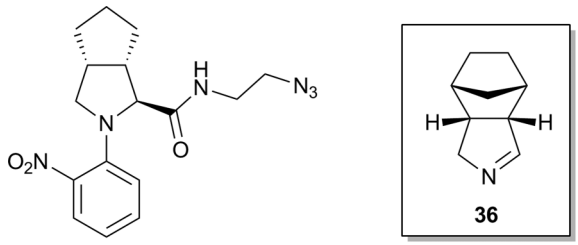


Fig. 3 Scope of Ugi-Smiles 3CR using enantiomerically enriched **32**. *Reagents and conditions*: (1*S*,4*R*)-3-azabicyclo-[3.3.0]oct-2-ene (**32**, 2.0 equiv.), (hetero)aromatic alcohol (1.0 equiv.), isocyanide (1.5 equiv.), MeOH, 40 °C, 24 h. Diastereomeric ratios were determined by ^{1}H NMR.



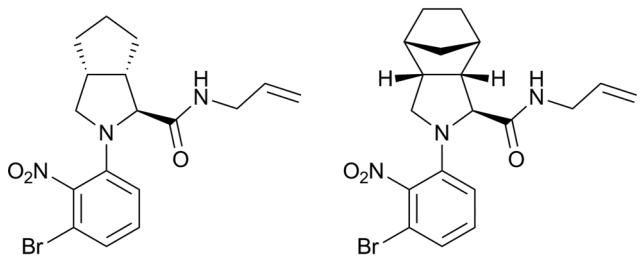


Fig. 4 Ugi-Smiles products with reactivity handles. *Reagents and conditions*: chiral cyclic imine (**32** or **36**, 2.0 equiv.), (hetero)aromatic alcohol (1.0 equiv.), isocyanide (1.5 equiv.), MeOH, 40 °C, 24 h. Diastereomeric ratios were determined by ^{1}H NMR.

multicomponent product. This phenomenon was only observed for compounds with the nitro substituent in a position *ortho* to the newly formed *N*-aryl bond. These compounds are likely highly rigid due to restricted rotation of the *N*-aryl bond. Further research regarding factors influencing these extraordinarily high specific rotations is ongoing.

Conclusions

We have developed an efficient combination of MAO-N-catalyzed desymmetrization of cyclic *meso*-amines with Ugi-Smiles multicomponent chemistry to generate optically pure *N*-aryl proline amides. This method represents the first report of a fully asymmetric Ugi-Smiles process. The simple procedure, broad substrate scope and the presence of diverse (heterocyclic) ring systems make these compounds highly attractive. Especially the possibility to add more diversity and complexity to these *N*-aryl proline amides by introducing strategic functional groups would make these products appealing for the design of synthesis of combinatorial libraries (*e.g.* better coverage of chemical space) of highly functionalized heterocyclic small molecules for the pharmaceutical industry.

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