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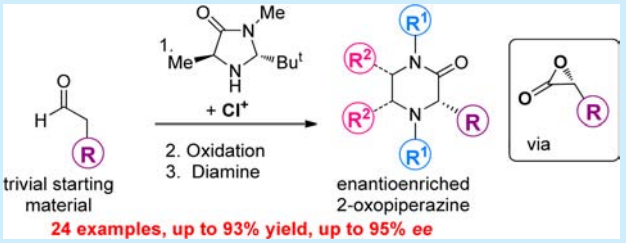
Enantioselective Organocatalytic Synthesis of 2-Oxopiperazines from Aldehydes: Identification of the Elusive Epoxy Lactone Intermediate

Nikolaos Kaplaneris, Constantinos Spyropoulos, Maroula G. Kokotou, and Christoforos G. Kokotos*

Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece

Supporting Information

ABSTRACT: An organocatalytic linchpin catalysis approach was envisaged to convert simple aldehydes into enantioenriched 2-oxopiperazines. A four-step reaction sequence (chlorination, oxidation, substitution, and cyclization) was developed and led to different substitution patterns in high yields and selectivities. The reaction mechanism was studied, and the previously elusive epoxy lactone intermediate was identified by HRMS.



The 2-oxopiperazine moiety constitutes a common structural motif in a number of pharmaceuticals and medicinally interesting natural products (Figure 1).[1] It

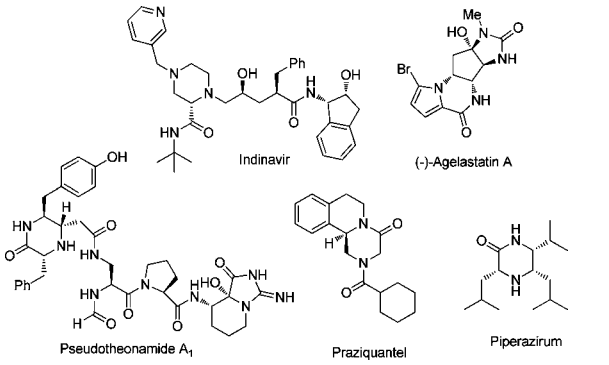


Figure 1. Natural products and pharmaceuticals bearing or derived from the 2-oxopiperzine core.

represents the structural core of several biologically active molecules, such as Leu-enkephalin analogues,[2a] cholecystokinin receptor antagonists,[2b] RGD mimetics,[2c] the neurokinin-2 receptor ligand,[2d] and promising candidates for the treatment of rheumatoid arthritis,[3a] depression,[3b] sexual dysfunction,[3c] and arterial thrombosis.[3d] Representative examples include the HIV protease inhibitor indivanir[4a] and the antischistosomiasis and soil-transmitted helminthiasis drug praziquantel[4b] (Figure 1).

For such an often-occurring moiety, one would expect a plethora of synthetic approaches. Unfortunately, until very recently, only approaches based on chiral pool techniques were available in the arsenal of a synthetic chemist.[5] This daunting challenge was recently addressed with complementary methods based on chiral-auxiliary-promoted dynamic resolutions[6] and multistep metal-catalyzed processes.[7] In 2015, Stoltz and co-workers reported an elegant palladium-catalyzed asymmetric allylic alkylation approach for the synthesis of chiral 2-oxopiperazines.[8]

Having been actively involved in the field of organocatalysis,[9] and in particular in the field of organocatalytic oxidation,[10] and being inspired by MacMillan's enantioselective linchpin SOMO catalysis,[11,12] we introduce herein the use of enamine-promoted linchpin catalysis for the enantioselective synthesis of 2-oxopiperazines[13] along with mechanistic investigations regarding the reaction outcome. A mild organocatalytic α-chlorination of heptanal (**1a**) was coupled with a selective oxidation, leading to chiral α-chloro acids in a single-flask operation. Nucleophilic substitution by *N*,*N*′-dibenzylethylenediamine (**3a**) can give rise to a substituted amino acid derivative that could be cyclized upon reaction conditions affording chiral 2-oxopiperazine **4a** (Table 1). This would summarize a four-step reaction sequence in just one operation, without requiring any intermediate purifications, that affords stereodefined molecules of increased molecular complexity beginning from trivial and cheap starting materials. From the available chlorination protocols,[11,14] a modified procedure utilizing MacMillan's third-generation catalyst **2** in conjunction with chloroquinone as the chlorinating agent[14a] led to a highly enantioselective and fast protocol that can be coupled with Pinnick oxidation to afford α-chloroheptanoic acid almost quantitatively. This chlorination protocol provides high levels of asymmetric induction and avoids postreaction epimerization. Treatment of this acid with diamine **3a** in a pressure vessel at 100 °C for 2 h led to a moderate yield of 2-oxopiperazine **4a** with 93% *ee* (entry 1). Increasing the amount of the diamine had a positive effect on the reaction yield (entry 2). Increasing or decreasing the reaction temperature did not improve the reaction outcome (entries 3 and 4 vs entry 2). It has to be noted that decreasing the reaction temperature led to a slight erosion of the

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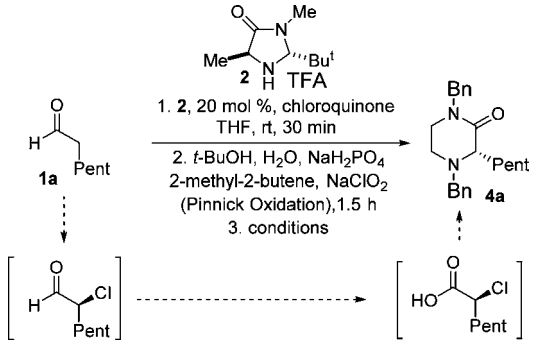
Table 1. Design Plan and Optimization of the Reaction Conditions Leading to Chiral 2-Oxopiperazines[a]



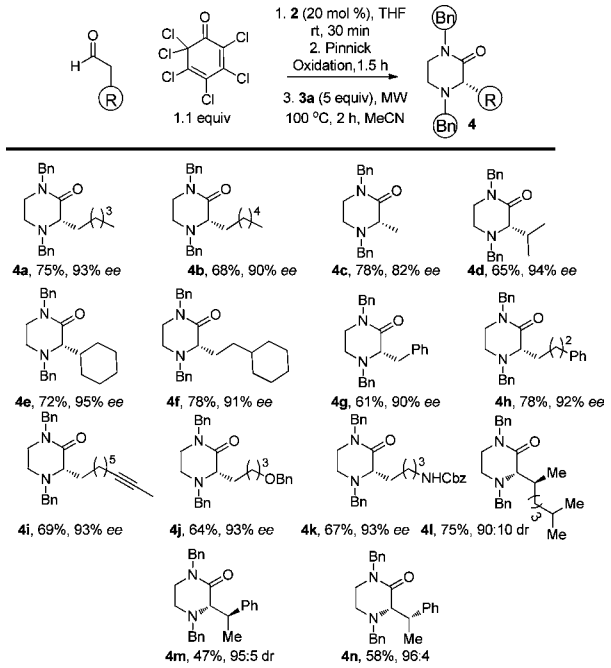
entry	conditions	yield (%)[b]	*ee* (%)[c]
1	$BnNHCH_2CH_2NHBn$ (3 equiv), 100 °C, 2 h	47	93
2	$BnNHCH_2CH_2NHBn$ (5 equiv), 100 °C, 2 h	57	93
3	$BnNHCH_2CH_2NHBn$ (5 equiv), 80 °C, 2 h	54	85
4	$BnNHCH_2CH_2NHBn$ (5 equiv), 120 °C, 2 h	56	92
5	$BnNHCH_2CH_2NHBn$ (5 equiv), 100 °C, MW, 2 h	75	93

[a]Catalyst **2** in THF, chloroquinone (1.1 equiv), heptanal (1 equiv) for 15 min at rt. *t*-BuOH, H_2O, 2-methyl-2-butene, $NaH_2PO_4.H_2O$, and $NaClO_2$ for 90 min at rt. Then MeCN and diamine. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

enantiointegrity of the product, which is due to competing mechanistic pathways, as will be discussed in detail later. Extending the reaction time led to a slight increase in the yield, but prolonging the reaction time (8 or 18 h) allows postepimerization to occur, leading to higher yields but significantly lower *ee*'s. Microwave irradiation constitutes a solution to this problem, since performing the reaction in a microwave reactor (entry 5) afforded the optimum reaction conditions, leading to the isolation of 2-oxopiperazine **4a** in 75% yield with 93% *ee*.

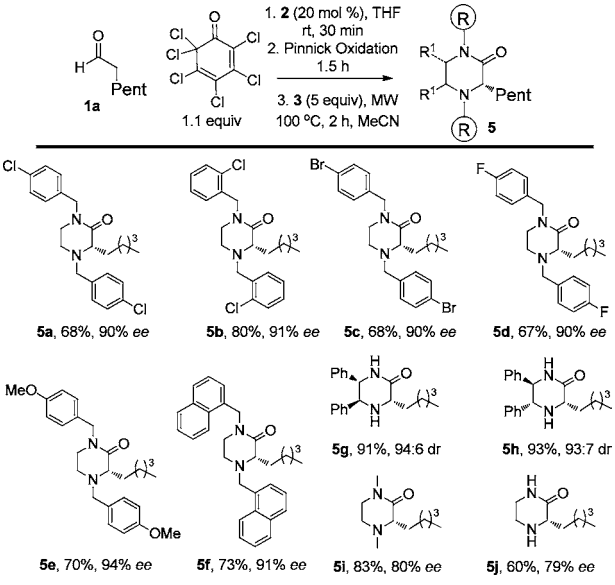
We next explored the scope of the aldehyde component. As highlighted in Scheme 1, a variety of functional groups can be readily tolerated on the aldehyde part. Linear aliphatic aldehydes led to high yields and enantioselectivities (**4a**–**c**), while branched aliphatic aldehydes, which are thought to be more sterically demanding, can also be employed, leading to similar high yields and selectivities (**4d**–**f**). A plethora of functional groups, such as aryl moieties, triple bonds, and protected alcohols and amines, can be employed without loss of reaction efficiency or enantiocontrol (**4g**–**k**). An additional chiral center at the β position of the carbonyl group could be problematic, since additional concerns regarding enamine formation, the geometry of the enamine formed, and whether there is substrate or catalyst control in the protocol would emerge. In these cases, the reaction time for chlorination step had to be increased (from 30 min to 1 h). When an aliphatic side chain was employed, the reaction yield remained high, but unfortunately a slight deterioration of the stereocontrol was observed (**4l**). On the other hand, when (*S*)- or (*R*)-3-phenylbutyraldehyde was employed, excellent enantiocontrol was observed, albeit in moderate yields (**4m**, **4n**). Thus, in the latter cases, the resident stereogenicity does not govern the generation of the stereocenter and the catalyst clearly plays a dominant role in the reaction outcome, demonstrating catalyst-directed induction rather than substrate-enforcing control.

Scheme 1. Enantioselective Synthesis of 2-Oxopiperazines: Aldehyde Substrate Scope



We then diverted our efforts to an exploration of the diamine substrate scope (Scheme 2). The substitution pattern on the aromatic moiety does not affect the reaction outcome (**5a**–**f**). Similarly as before, treatment of the chiral α-chloro acid with either (1*S*,2*S*)- or (1*R*,2*R*)-diphenylethylenediamine led to the incorporation of three chiral centers on the 2-oxopiperazine skeleton with high stereocontrol in excellent yields (**5g**, **5h**). One limitation of the current protocol is that decreased enantioselectivities are observed when diamines that do not possess an aromatic moiety are utilized (**5i**, **5j**).

Scheme 2. Enantioselective Synthesis of 2-Oxopiperazines: Diamine Substrate Scope



In order to determine the absolute configuration of the product, commercially available Boc-Phe-OH (**6**) was con-

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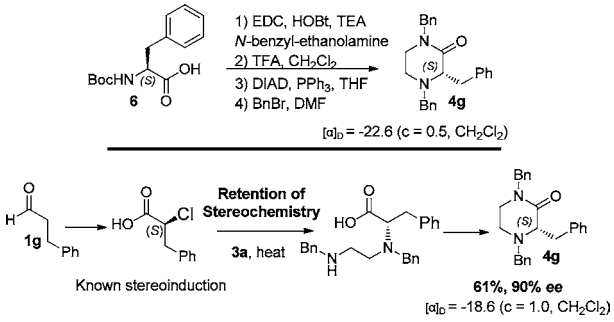
verted to (*S*)-2-oxopiperazine **4g** (Scheme 3). Initially, amide bond formation followed by Boc deprotection led to an amino

Scheme 3. Determination of the Absolute Configuration of the Product



alcohol, which was used in a Mitsunobu reaction to ensure cyclization followed by benzylation. This linear sequence of reactions led to (*S*)-**4g**, for which $[\alpha]_D = -22.6$ ($c = 0.5$, CH_2Cl_2). It is known that imidazolidinone catalyst **2** provides (*S*)-2-chloroheptanoic acid.[11,12] Since 2-oxopiperazine **4g**, obtained from (*S*)-2-chloroheptanoic acid, has the same absolute stereochemistry [(*S*)], the direct S_N2 reaction pathway is not operative, and thus, a different mechanistic pathway is followed that leads to retention of the stereochemistry. Usually retention of stereochemistry occurs when a neighboring effect is in place. In this case, the carboxylic group, which is in close proximity, displaces the chloride, leading to a highly labile and transient epoxy lactone intermediate, which in turn is attacked by the diamine to afford the desired amino acid with retention of stereochemistry, relieving it from its strain.

To probe this reaction mechanism, we decided to study the displacement and the cyclization reaction by ESI (positive ionization mode) high-resolution mass spectrometry (HRMS). Epoxy lactone intermediates have been postulated as active species when retention of stereochemistry occurs next to a carboxylic group,[15] but because of their labile nature, they have never been detected or isolated. In fact, only doubly substituted epoxy lactones, whose stability is favored because of the electronic nature of their substituents, leading to longer lifetimes, have been identified by IR spectroscopy.[16] In contrast, monosubstituted epoxy lactones are considered to be highly reactive and have never been identified. We initiated our study by employing 2-chloroheptanoic acid in MeCN and 5 equiv of diamine **3a**. When the reaction mixture was heated at 100 °C, the epoxy lactone intermediate was identified (Figure 2).[17] The reaction was performed in MeCN utilizing conventional heating equipped with a condenser. After 20 or 80 min, a peak corresponding to epoxy lactone was clearly detected in the reaction mixture (Figure 2), while at the end of the reaction, product **4a** was observed. It has to be highlighted that after 80 min, the product of the substitution reaction of the chloride by the diamine was also observed. In addition, the product derived from the amidation reaction (which still bears the chloride) could not be observed. Thus, without any doubt, the substitution reaction occurs first, followed by the cyclization step. Going back to the HRMS study, after 20, 40, 60, and 80 min, the epoxy lactone intermediate, although a rather short-lived species, was detected in the reaction mixture when the reaction was carried out at 100 °C.[17] Throughout the study of the reaction by HRMS, special care had to be taken (reaction

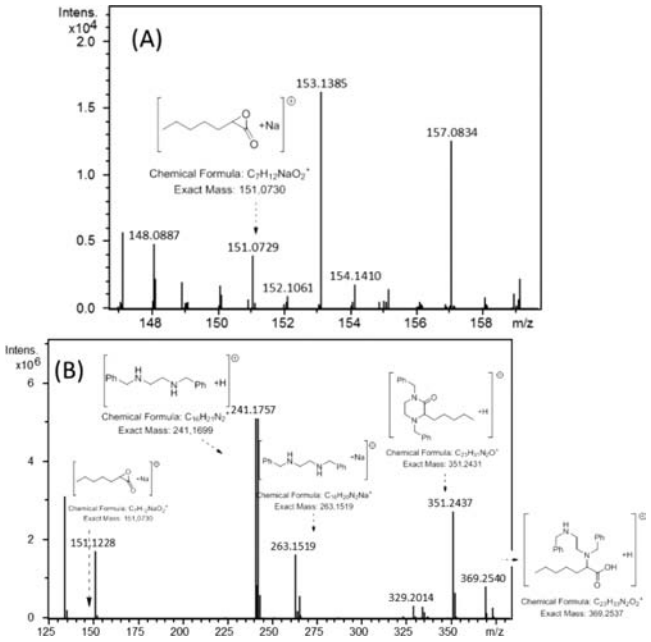


Figure 2. Direct detection of the epoxy lactone intermediate. Shown are HRMS spectra of the reaction of 2-chloroheptanoic acid in MeCN with 5 equiv of diamine **3a** at 100 °C for reaction times of (A) 20 min and (B) 80 min.

carried out next to the HRMS instrument, fast dilution with hot MeCN, immediate HRMS run in a total time of few seconds) in order to observe the epoxy lactone.[18] Delaying the whole process by a few seconds led to reaction or consumption of the epoxy lactone toward product formation, having as a direct consequence the failure to observe the intermediate. Thus, very fast and thorough experimentation was required for the identification of such a labile species. When the reaction was performed at room temperature, the epoxy lactone intermediate was not observed. Similarly, just heating of 2-chloroheptanoic acid led to no detection of the epoxy lactone. The two competing reaction mechanisms, the direct S_N2 reaction and the epoxy lactone mechanism, which lead to opposite enantiomers, have distinct reaction conditions that are operative. At 100 °C, the epoxy lactone mechanism dominates, leading to the product with retention of stereochemistry in high degree. Decreasing the reaction temperature has the consequence that the direct S_N2 pathway starts to compete with the epoxy lactone pathway, leading to lower enantiomeric excess of the product. At high temperature, the epoxy lactone mechanism outperforms the inversion pathway, while at room temperature, the two pathways have similar activation energy and the enantiomeric excess observed is low. In addition, performing the reaction at rather elevated temperatures (above 100 °C) leads to slight erosion of the enantioinduction.

In conclusion, an organocatalytic enamine-based protocol for the asymmetric generation of 2-oxopiperazines from aldehydes is described. Four efficient and consecutive transformations, without the need for intermediate purification, occur to provide a linchpin process. A broad substrate scope is described with respect to the aldehyde and the diamine skeleton, leading to polyfunctionalized motifs often present in numerous pharmaceuticals, enzyme inhibitors, and β-turn structures. Finally, the process provides the final product with retention of the stereochemistry due a neighbor carboxylate group. The elusive and short-lived epoxy lactone intermediate, which has been

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suggested in the literature to account for this retention but has never been characterized and identified, was detected using HRMS. This study constitutes the first successful example of observing this epoxy lactone intermediate, verifying the hypothesis that has been proposed in the past. This cultivates the notion that HRMS analysis is a powerful technique for the identification and observation of hypothesized species.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02699.

Experimental procedures, full optimization data, characterization data, NMR spectra, HPLC traces, and HRMS experiments and conditions (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ckokotos@chem.uoa.gr

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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(17) For further comments and reaction setup for the HRMS mechanistic experiments, see the Supporting Information.

(18) The epoxy lactone intermediate is quite short-lived. After a few seconds, it reacts and is no longer visible by HRMS. Attempts to identify the epoxy lactone by NMR spectroscopy were not successful, probably because of the low concentration of the intermediate coupled with its short lifetime.

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