Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201701386

Link to VoR: http://dx.doi.org/10.1002/adsc.201701386

10.1002/adsc.201701386

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Organocatalytic Synthesis of Oxazolines and Dihydrooxazines from Allyl-Amides: Bypassing the Inherent Regioselectivity of the Cyclization

Alexis Theodorou,[a] Ierasia Triandafillidi[a] and Christoforos G. Kokotos[a]*

[a] Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece
Fax.: (+30) 2107274761; Phone: (+30) 2107274281; email: ckokotos@chem.uoa.gr

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

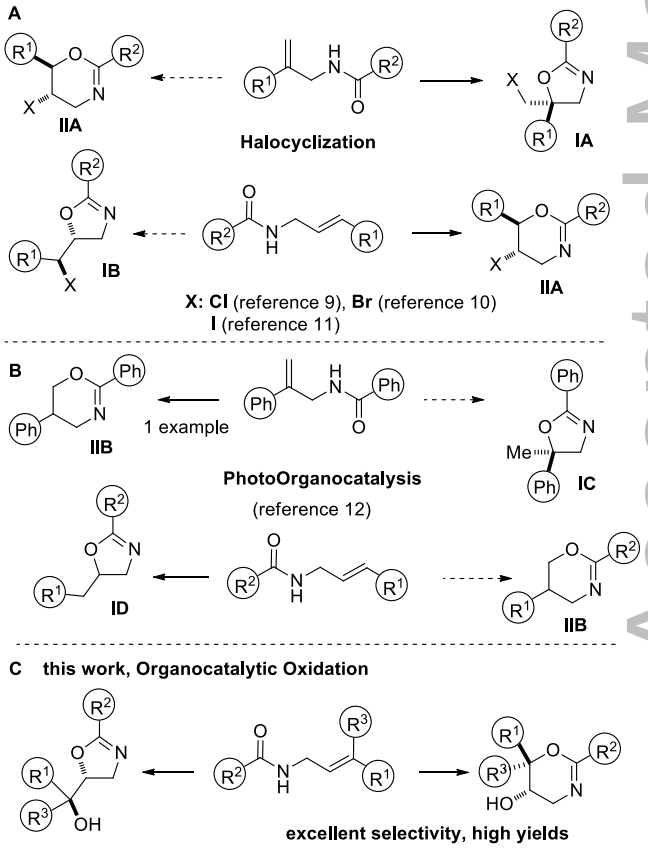
Abstract. A selective and efficient methodology for the construction of either oxazolines or dihydrooxazines from the corresponding allyl-amides is reported. Bypassing the inherent selectivity of the cyclization and depending on the substitution pattern of the substrate, a selective epoxidation-cyclization was developed leading to either the five-membered or the six-membered ring, upon simple and complementary reaction conditions. The cyclization products were obtained in good to excellent yields and high selectivities.

Keywords: Organocatalysis, Oxidation, Green chemistry, Oxazolines, Dihydrooxazines

Introduction

Oxazolines and dihydrooxazines are heterocycles that are commonly encountered in a variety of natural products, pharmaceuticals and chiral ligands. In particular, oxazoline is an important scaffold, which is present in numerous natural products,[1] molecules of biological importance exhibiting antitumor,[2a] anticancer,[2b] antidepressant[2c] and antibacterial properties.[2d] Furthermore, oxazolines and dihydrooxazines play a pivotal role in protecting groups,[3] chiral ligands and auxiliaries.[4] Due to their significant importance, a variety of routes have been reported for their syntheses, starting from aldehydes,[5] carboxylic acids and their derivatives,[6] olefins[7] and hydroxy-amides.[8] Among the most important synthetic routes to construct either oxazolines or dihydrooxazines is the cyclization of allyl-amides (Scheme 1).

The most common reaction pathway constitutes the halocyclization of allyl-amides (Scheme 1, **A**).[9-11] Firstly, the bromination reaction was explored,[10a] while later a variety of asymmetric approaches were developed for the corresponding chlorination,[9] bromination[10] and iodination.[10b,11] However, in all cases, there is an inherent regioselectivity for the cyclization step that cannot be suppressed. When a 1,1-disubstituted alkene is employed, the oxazoline derivative **IA** is obtained and no dihydrooxazine **IIA** can be produced (Scheme 1, **A** top).



Scheme 1. Approaches for the synthesis of oxazolines and dihydrooxazines from allyl-amides.

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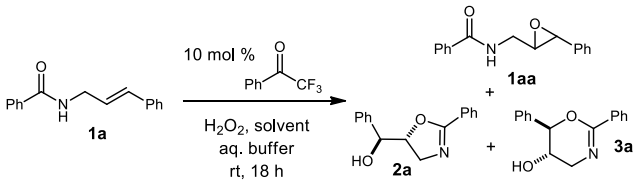
The cyclization follows Baldwin's empirical cyclization rules. In addition, when the alkene is 1,2-disubstituted, the corresponding dihydrooxazine **IIA** is produced and no oxazoline **IB** is observed (Scheme 1, **A** bottom). In this case, cyclization occurs on the carbon atom, where additional stabilization is favored via the neighboring groups, leading selectively to the six-membered ring. Thus, there is a gap in literature reports regarding the selective synthesis of these substrates from the same starting material. In an effort to bridge this gap, Nicewicz and Morse reported an alternative approach employing PhotoOrganocatalysis for the photoredox hydrofunctionalization of allyl-amides (Scheme 1, **B**).[12] They reported a single example transforming a 1,1-disubstituted alkene into dihydrooxazine **IIB**, not observing any oxazoline **IC** (Scheme 1, **B** top). Furthermore, 1,2-disubstituted allyl-amides were transformed selectively to oxazolines **ID** (Scheme 1, **B** bottom). Although this elegant contribution provided a complementary solution, the problem of overcoming the inherent regioselectivity of the cyclization still stands unsolved. Herein, we would like to report our efforts into providing a general, easily executable and unified solution bypassing this inherent regioselectivity of the cyclization (Scheme 1, **C**). Our protocol involves the selective epoxidation of allyl-amides, employing hydrogen peroxide as the green oxidant and an organocatalyst to activate hydrogen peroxide, followed by selective cyclization to either the five-membered ring oxazoline or the six-membered ring dihydrooxazine.

Results and Discussion

Previously, we were engaged in developing a novel organocatalytic oxidative protocol that could employ hydrogen peroxide as the oxidant.[13] Hydrogen peroxide is a green and environmentally friendly oxidant, since its only byproduct is water. However, its poor oxidation power requires its activation by a catalyst. Normally, this is realized by the use of a metal catalyst, which is associated with high toxicity and waste production. A few years ago, we identified 2,2,2-trifluoroacetophenone as the appropriate organocatalyst for hydrogen peroxide activation. We initially demonstrated its use in the oxidation of heteroatoms, like silanes,[13a] tertiary amines and azines,[13b,c] sulfides[13d] and anilines, where we studied also the reaction mechanism, excluding the possibility of the involvement of a dioxirane intermediate.[13e] Also, we have employed this oxidative protocol in the oxidation of alkenes and cyclization reactions.[14] In this work, our environmentally friendly protocol provides a new, cheap and easy to perform synthetic pathway to

Table 1. Optimization of the reaction conditions.



Entry	Catalyst (mol%)	Solvent	Yield **1aa** (%)[a]	Yield **2a** (%)[a]	Yield **3a** (%)[a]
1	10	tBuOH	65	5	17
2	10	MeCN	48	12	35
3	10	AcOEt	65	7	16
4[b]	20	MeCN	>99	-	-

[a] The conversion was calculated by ^{1}H-NMR. [b] The oxidation step was left stirring for 4 h instead of 18 h.

oxazolines and dihydrooxazines, bypassing the inherent regioselectivity encountered in the cyclization step.

We began our investigation by employing allyl-amide **1a** in our general reaction conditions for the epoxidation (Table 1, entry 1). Interestingly, although epoxide **1aa** was the major product, both oxazoline **2a** and dihydrooxazine **3a** were formed. This result intrigued us in finding the appropriate reaction conditions to provide either **2a** or **3a**. Simple alteration of the solvent did not improve the selectivity of the reaction (Table 1, entries 1-3). Increasing the catalyst loading and carefully studying the reaction conditions led to a quantitative yield of epoxide **1aa** (Table 1, entry 4).

We then turned our attention into bypassing the inherent regioselectivity of the reaction, which leads to the formation of the five-membered ring **2a**, according to literature reports and Baldwin's empirical rules (Table 2). Having previous experience in imposing anti-Baldwin cyclizations[15] and hypothesizing that an interaction of the intermediate epoxide with a Lewis acid could alter the cyclization towards the six-membered ring, a variety of acidic conditions were tested (Table 2, entries 1 and 2). From a variety of choices, the use of cheap and extremely common trifluoroacetic acid (TFA) and camphorsulfonic acid (CSA) provided a quantitative yield of dihydrooxazine **3a**. The use of common Bronsted acids was preferred, in order to provide a more general and cheap protocol. We then turned our attention into identifying the appropriate basic additive to provide a protocol for the synthesis of oxazoline **2a** (Table 2, entries 3-6). From some common bases, tBuOK afforded a quantitative yield in short reaction time at slightly elevated temperature. Performing the reaction at room temperature required prolonged reaction time to reach to the same

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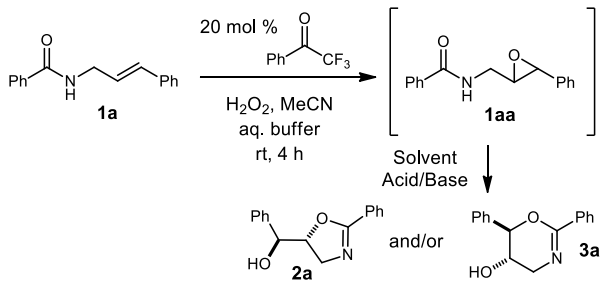
Table 2. Optimization of the reaction conditions.[a)]



Entry	Solvent	Acid/ Base	T (°C), Time (h)	Yield **2a** (%)[b)]	Yield **3a** (%)[b)]
1	CH_2Cl_2	CSA	rt, 18	-	>99
2	CH_2Cl_2	TFA	rt, 1.5	-	>99
3	CH_2Cl_2	Cs_2CO_3	rt, 18	14	31
4	THF	NaH	rt, 18	30	-
5	CH_2Cl_2	DBU	rt, 18	0	0
6	CH_2Cl_2	^{t}BuOK	50, 1.5	>99	-

[a)] **1a** (0.30 mmol) in MeCN, $PhCOCF_3$ (0.06 mmol), aq buffer and H_2O_2 at rt for 4 h, then solvent, acid/base. [b)] The conversion was calculated by ^{1}H-NMR.

outcome. In this manner, we could provide two direct manifolds starting from an allyl-amide and depending on the reaction conditions adopted to impose the mode of cyclization that is preferred.

Having established the optimum reaction conditions, we turned our attention to the exploration of the substrate scope (Table 3). Starting from allyl-amide **1a**, oxazoline **2a** was isolated in 78% yield, while the dihydrooxazine **3a** was isolated in 74% yield (Table 3, entry 1). No other product (starting material or epoxide) was observed in either case. It has to be noted that in order to be certain for both the regioselectivity of the cyclization step, as well as the relative stereochemistry of the product, structures **2a** and **3a** were analyzed with literature precedent (*syn*-derivatives), whose structures have been proven via X-ray crystallography.[16] Changing the substitution pattern and the electron density of the aromatic moiety of the amide did not alter the inherent selectivity of the cyclization step leading to five-membered oxazolines **2b-e**, **2h** and **2i** in good to high yields (Table 3, entries 2-5, 8 and 9). Bypassing this selectivity, the acidic conditions after the epoxidation step led to six-membered dihydrooxazines **3b-e**, **3h** and **3i** (Table 3, entries 2-5, 8 and 9). Moving from aromatic substituents to aliphatic moieties on the amide required additional base and elevated reaction temperature to ensure cyclization. Indeed, oxazolines **2f** and **2g** were prepared in moderate yields (Table 3, entries 6 and 7). Unfortunately, all attempts for the synthesis of dihydrooxazines failed to deliver the desired product (Table 3, entries 6 and 7). The only isolated product was the epoxide, which even after prolonged reaction time and/or heating did not lead to the dihydrooxazine. The electron density of the aryl substituent of the allyl moiety was of great importance for the outcome of the reaction, since the strongly electron rich *para*-methoxy group led to a selective ring opening-six-membered ring formation, upon the epoxidation reaction conditions (Table 3, entry 10). All attempts to isolate the intermediate epoxide met with failure. This did not leave any room for selective manipulation on the cyclization step. The substituent on the aryl moiety on the allyl component of the starting material proved to be of quite crucial importance, since the corresponding *para*-nitro and *para*-chloro derivatives were insoluble in the reaction mixture and failed to provide the reaction. In an effort to gain further mechanistic insight of the reaction sequence, *E*- and *Z*-trisubstituted allyl-amides **1k** and **1l** were tested, respectively (Table 3, entries 11 and 12). Under the basic conditions of the oxazoline synthesis, **1k** afforded oxazoline **2k** as a single diastereomer, verifying our hypothesis and literature knowledge, that after the regioselective epoxidation, a common S_N2 reaction mechanism for the ring opening-cyclization occurs, according to Baldwin's cyclization rules. In accordance with this, *Z*-allyl-amide **1l** afforded oxazoline **2l**, the diastereomer of **2k**. Under the acidic conditions of the dihydrooxazine synthesis, there are a number of alternative proposed cyclization mechanisms that could be in place. For instance, if the epoxide intermediate is activated by the Bronsted acid, with an interaction, similar to Lewis acid activation of epoxides, one could assume a stable benzylic carbocation is formed, which upon cyclization can lead to the same product, no matter of the nature of the double bond (*E*-, *Z*- or mixture) of the starting material. This is not the case, since a different diastereomer of the dihydrooxazine was obtained (**3k** and **3l**, respectively). It seems that activation of the epoxide with the Bronsted acid occurs, and then a simultaneous ring opening-cyclization (S_N2-type) takes place to afford the TFA salt of the dihydrooxazine, which upon wash with aq. $NaHCO_3$ affords the desired dihydrooxazine.[17] In the former case, only dihydrooxazine **3k** was obtained in high yield (Table 3, entry 11). In the latter case, a mixture of dihydrooxazine **3l** and oxazoline **2l** was isolated (Table 3, entry 12). We believe that the stereochemical hindrance on **3l** (hydroxy group is *cis* to the phenyl ring) is the limiting factor for the selective synthesis of dihydrooxazine (*anti*-Baldwin) and in retrospect leads to cyclization via the Baldwin-selective 5-*exo*-*tet* to oxazoline **2l**. Unfortunately, moving to 1,1-disubstituted allyl-amides, like **1m**,

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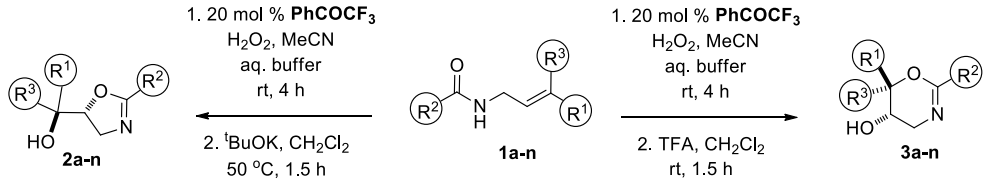
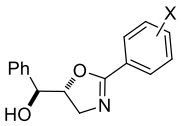
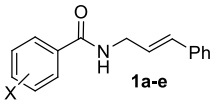
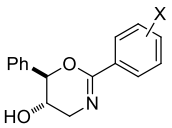
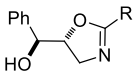
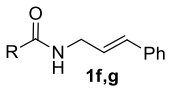
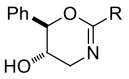
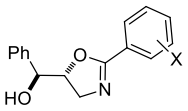
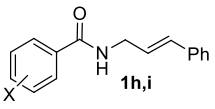
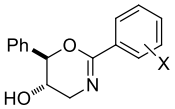
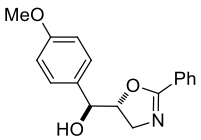
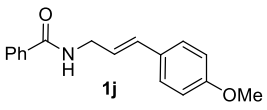
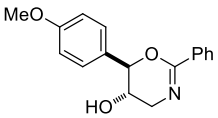
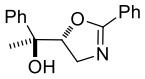
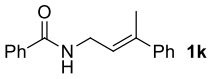
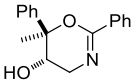
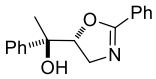
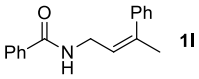
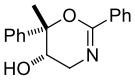
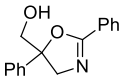
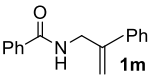
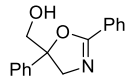
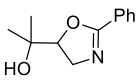
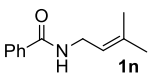
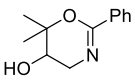
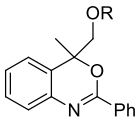
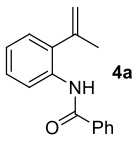
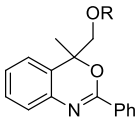
Table 3. Substrate scope of the organocatalytic synthesis of oxazolines or dihydrooxazines from allyl-amides.[a)]



Entry	Product	Yield (%)[b)]	Starting Material	Product	Yield (%)[b)]
1		X: H **2a**, 78%			X: H **3a**, 74%
2		X: *p*-Br **2b**, 85%	 **1a-e**		X: *p*-Br **3b**, 80%
3		X: *p*-CF_3 **2c**, 85%			X: *p*-CF_3 **3c**, 84%
4		X: *p*-NO_2 **2d**, 55%			X: *p*-NO_2 **3d**, 73%
5		X: *o*-Cl **2e**, 83%			X: *o*-Cl **3e**, 84%
6[c)]		R Bn **2f**, 46%	 **1f,g**		R Bn **3f**, -
7[d)]		R: n-C_7H_{15} **2g**, 65%			X: n-C_7H_{15} **3g**, -
8		X: *p*-MeO **2h**, 80%	 **1h,i**		X: *p*-MeO **3h**, 84%
9		X: *2,4*-diMe **2i**, 55%			X: *2,4*-diMe **3i**, 62%
10[e)]		**2j**, -	 **1j**		**3j**, 57%
11		**2k**, 83%	 **1k**		**3k**, 72%
12		**2l**, 78%	 **1l**		**3l+2l**, 77% (42:58)
13		**2m**, 87%	 **1m**		**2m**, 97%
14		**2n**, 90%	 **1n**		**3n+2n**, 86% (60:40)
15		R : H **5a**, 99%	 **4a**		R : H **5a**, 99%
16[f)]		R : Ac **5b**, 71%			-

[a)] **1a** (0.30 mmol) in MeCN (0.24 mL), $PhCOCF_3$ (0.06 mmol), aq. buffer (0.24 mL, 0.6M K_2CO_3 – 4 x 10^{-4}M EDTA disodium salt), acetonitrile (0.30 mL) and 30% aqueous H_2O_2 (0.84 mL) at rt for 4 h, then for oxazolines: dry THF (3 mL), KO^{t}Bu (0.45 mmol) at 50 °C for 90 min; for dihydrooxazines: dry CH_2Cl_2 (3 mL), TFA (0.60 mmol) at rt for 90 min, then wash with aq. $NaHCO_3$. [b)] Isolated yield. [c)] KO^{t}Bu (1.20 mmol) at 70 °C for 90 min. [d] KO^{t}Bu (0.60 mmol) at 70 °C for 90 min. [e] Cyclization occurred during the oxidation step. [f] EtOAc instead of THF was used as the solvent for the cyclization step.

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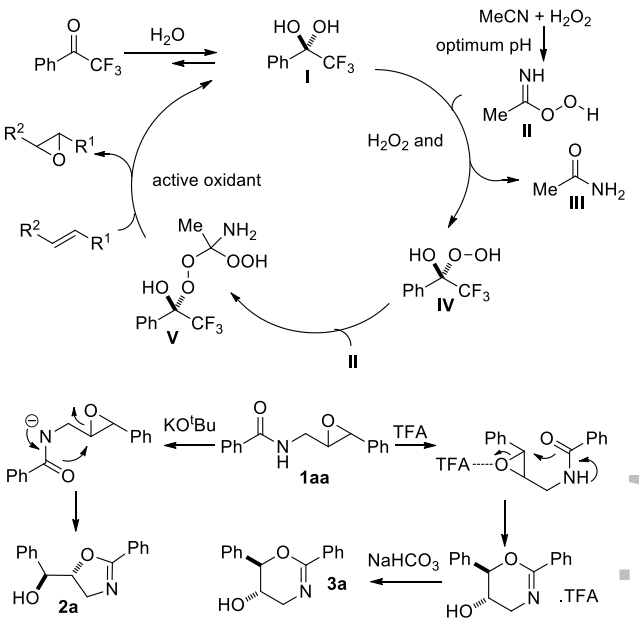
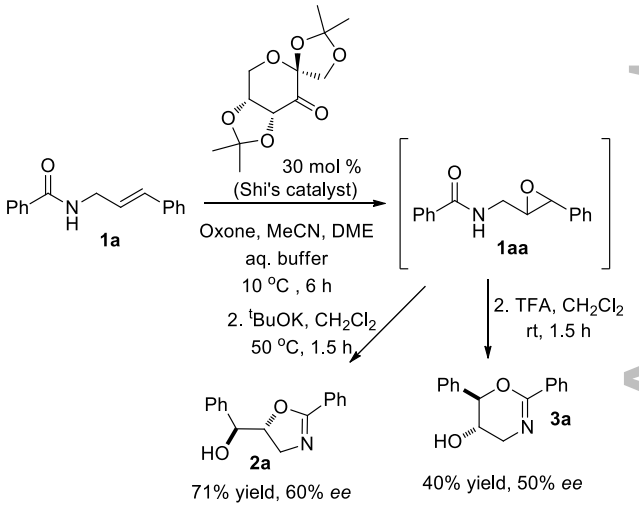
and although the intermediate epoxide was formed, under both acidic or basic conditions, oxazoline **2m** was the sole product obtained (Table 3, entry 13). In the former case, an almost quantitative yield was obtained. The outcome of the reaction was expected, although it did not provide the possibility for selection of the reaction pathway. Under basic conditions, the Baldwin rules were followed, as well as ring opening at the most hindered side. Under the acidic conditions, the ring opening and cyclization occurs at the side, where the slightly positive charge is stabilized. When trisubstituted allyl-amide **1n** was employed, oxazoline **2n** was obtained in high yield (Table 3, entry 14). Under acidic conditions, the desired dihydrooxazine **3n** was formed, albeit as a mixture with oxazoline **2n** (Table 3, entry 14). As before, the additional steric hindrance of the *gem*-methyl substituents next to the hydroxy group (one methyl is *cis* and the other is *trans*) apparently increases the energy required for cyclization and thus, oxazoline **2n** was also formed. This result also hints that the cyclization and the selectivity observed in the cases of aromatic substituted allyl-amides (for example, **3k** vs **3n**) are controlled by the stabilization of the benzylic "*quasi*" carbocation. Moving to another example of 1,1-disubstituted olefin, allyl-amide (vinylphenyl amide) (**4a**), under both reaction conditions, the same product (**5a**) was isolated in a quantitative yield (Table 3, entry 15). As expected, under acidic conditions the six-membered ring was formed. However, under basic reaction conditions, the attack on the less hindered face of the epoxide that would lead to an unfavorable seven-membered ring was not followed, and thus, the more thermodynamically stable six-membered ring was formed. Interestingly, when EtOAc was employed as the solvent for the cyclization step, acetylated product **5b** was formed (Table 3, entry 16).

Based on our previous studies[14] and current experiments, a proposed reaction mechanism is shown in Scheme 2. In the aqueous environment of the reaction, 2,2,2-trifluoroacetophenone affords diol **I**. Then, and in the appropriate pH, MeCN reacts with H_2O_2 to afford **II**, which in conjunction with H_2O_2 oxidizes **I** to perhydrate **IV**.[14] Another molecule of **II** reacts with **IV** affording **V**, which can be or provide the active oxidant of the protocol, which epoxides the allyl-amide.[13e] Under basic conditions, Baldwin's cyclization rules are followed and cyclization at the least hindered position leads to the formation of oxazolines. Under acidic conditions, activation of the epoxide, leads to the simultaneous ring opening-cyclization on the side that stabilizes better the formed carbocation leading to dihydrooxazines.



Scheme 2. Proposed reaction mechanism.

Finally, attempts were made to provide an asymmetric manifold. Since all our efforts to introduce a chiral catalyst for this protocol (employing hydrogen peroxide) proved unsuccessful, we turned our attention into the well-established dioxirane chemistry.[18] Utilizing Shi's catalyst and Oxone as the oxidant, we were able to render the process asymmetric (Scheme 3). In unoptimized reaction conditions, oxazoline **2a** was obtained in 71% yield and 60% *ee*, while **3a** was obtained in 40% yield and 50% *ee*.



Scheme 3. Asymmetric variant.

Conclusion

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In conclusion, an efficient and selective protocol for the synthesis of oxazolines or dihydrooxazines from the corresponding allyl-amides was introduced. Bypassing the inherent selectivity of the cyclization, which depends on the substitution pattern of the substrate, the selective epoxidation-cyclization was performed leading to either the five-membered or the six-membered ring, upon simple and complementary reaction conditions. The cyclization products were obtained in good to excellent yields and high selectivities. Attempts to render the process asymmetric, met with limited success.

Experimental Section

General Procedure for the Organocatalytic Synthesis of 2-Oxazolines: Substrate (0.30 mmol) was placed in a round bottom flask and dissolved in MeCN (0.24 mL). 2,2,2-Trifluoro-1-phenylethanone (8.7 mg, 0.05 mmol), aqueous buffer solution (0.24 mL, 0.6M K_2CO_3 – 4 x 10^{-4} M EDTA disodium salt), acetonitrile (0.30 mL, 6.00 mmol) and 30% aqueous H_2O_2 (0.84 mL, 8.00 mmol) were added consecutively. If the substrate is insoluble to the reaction mixture, EtOAc (0.1 mL) was added as well. The reaction mixture was left stirring for 4 hours at room temperature. The reaction was diluted with CH_2Cl_2 (5 mL) dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure up to 30 ^oC, to give the crude epoxide intermediate. Then, the reaction mixture was dissolved in dry THF (3 mL). KO^{t}Bu (50 mg, 0.45 mmol) was added and the reaction mixture was left stirring at 50 ^oC for 90 min. The solvent was evaporated, EtOAc (5 mL) was added and the residue was filtered off. The filtrate was then concentrated under reduced pressure and the crude product was purified using flash column chromatography (40% EtOAc in Pet. Ether) to afford the desired product.

Procedure for the Organocatalytic Synthesis of Dihydro-1,3-Oxazines: Substrate (0.30 mmol) was placed in a round bottom flask and dissolved in MeCN (0.24 mL), 2,2,2-Trifluoro-1-phenylethanone (8.7 mg, 0.05 mmol), aqueous buffer solution (0.24 mL, 0.6M K_2CO_3 - 4x10^{-4}M EDTA disodium salt), acetonitrile (0.30 mL, 6.00 mmol) and 30% aqueous H_2O_2 (0.84 mL, 8.00 mmol) were added consecutively. If the substrate is insoluble to the reaction mixture, EtOAc (0.1 mL) was added as well. The reaction mixture was left stirring for 4 hours at room temperature. The reaction was quenched with CH_2Cl_2 (5 mL) dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure up to 30 ^oC, to give the crude intermediate epoxide. Then, the reaction mixture was dissolved in dry CH_2Cl_2 (3 mL). TFA (46 μL, 0.60 mmol) was added and the reaction mixture was left stirring at room temperature for 90 min. The solvent was evaporated, EtOAc (10 mL) was added and the organic layer was washed with aq. $NaHCO_3$ (10 mL, 10% w/w). The organic layer was dried (Na_2SO_4), filtered and concentrated and the crude product was purified using flash column chromatography (40% EtOAc in Pet. Ether) to afford the desired product.

Acknowledgements

The authors gratefully acknowledge the Operational Program "Education and Lifelong Learning" for financial support through the NSRF program "ΕΝΙΣΧΥΣΗ ΜΕΤΑΔΙΔΑΚΤΟΡΩΝ ΕΡΕΥΝΗΤΩΝ" (PE 2431)" co-financed by ESF and the Greek State. The authors would also like to thank Konstantinos Doukas and Vassileios Mouchtouris for preliminary results and Dr. Maroula Kokotou for her assistance in acquiring HRMS data. IT would like to thank the Hellenic Foundation of Research and Innovation (ΕΛΙΔΕΚ) for a PhD scholarship. Also, COST Action C-H Activation in Organic Synthesis (CHAOS) CA15106 is acknowledged for helpful discussions.

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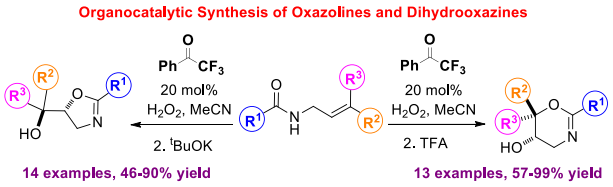
10.1002/adsc.201701386

FULL PAPER

Organocatalytic Synthesis of Oxazolines and Dihydrooxazines from Allyl-Amides: Bypassing the Inherent Regioselectivity of the Cyclization

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Alexis Theodorou, Ierasia Triandafillidi, Christoforos G. Kokotos*



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