Stereoselective Oxidative Cyclization of *N*-Allyl Benzamides to Oxazolines

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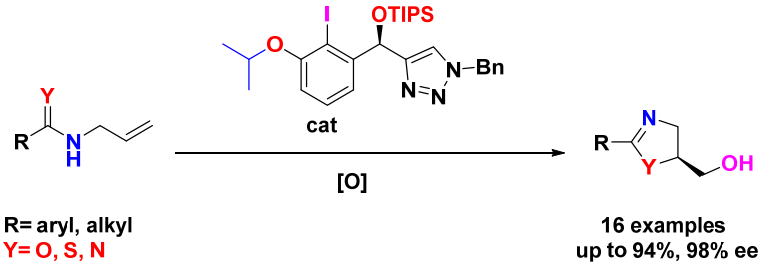
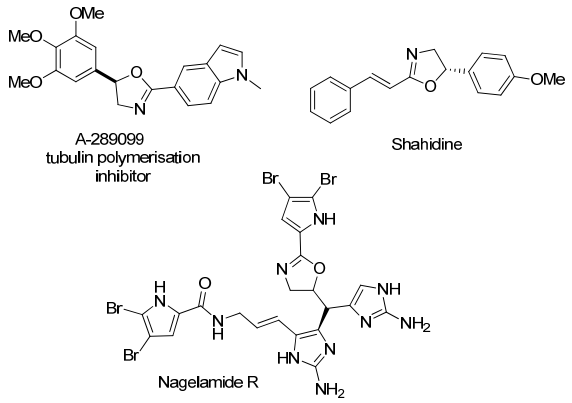
KEYWORDS: Oxazolines, Hypervalent Iodine, Cyclisation, Enantioselective Oxidation, Derivatizations

ABSTRACT: This study presents an enantioselective oxidative cyclization of *N*-allyl carboxamides via a chiral triazole-substituted iodoarene catalyst. The method allows the synthesis of highly enantioenriched oxazolines and oxazines, with yields of up to 94% and enantioselectivities of up to 98% ee. Quaternary stereo centers can be constructed and, besides *N*-allyl amides, the corresponding thioamides and imideamides are well tolerated as substrates, giving rise to a plethora of chiral 5-membered *N*-heterocycles. By applying a multitude of further functionalizations, we finally demonstrate the high value of the observed chiral heterocycles as strategic intermediates for the synthesis of other enantioenriched target structures.



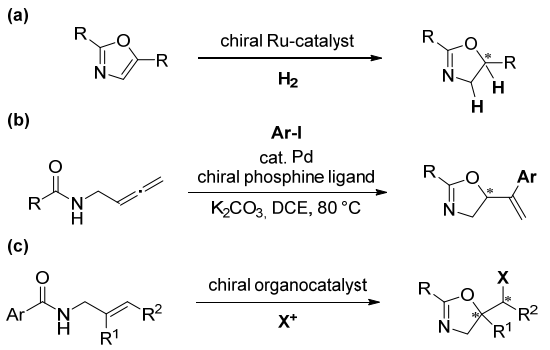
Partially hydrogenated *N*-heterocycles (azolines), in particular 2-oxazolines, 2-thiazolines, and 2-imidazolines, are important synthetic targets, not only due to their abundance in biologically active compounds,[1–7] but also due to their high value as useful synthetic building blocks.[8–13] Enantiopure derivatives substituted either at C4, at C5, or at both saturated carbons are of particular importance due to the stereochemical requirements of the desired products or the chiral building blocks made by them. Enantiopure 4-oxazolines are also widely applied as core structural motifs, for example in chiral ligands for enantioselective transition metal-catalyzed reactions.[14–18]

Figure 1. Examples of natural products containing a chiral C5-substituted oxazoline unit.



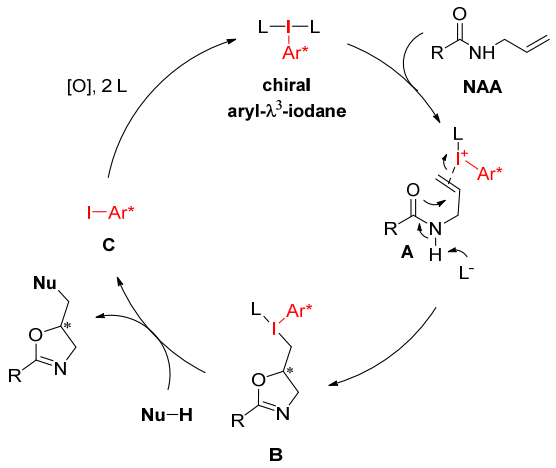
Enantiopure 5-oxazolines are found in biological active compounds such as shahidine – the parent compound of the strong antioxidant aegilin,[19] nagelamide alkaloids,[20] and the tubulin-binder A289099 (Figure 1).[2] While synthetic approaches for 4- and 4,5-disubstituted chiral 2-azolines are well established,[10,11,21,22] the synthesis of enantiopure monosubstituted 5-azolines is underdeveloped (Scheme 1).[23–29] The latter can be synthesized by Ru-catalyzed hydrogenations of oxazoles (Scheme 1 (a))[30] or by Pd-catalyzed cyclizations of allene-substituted aryl amides (Scheme 1 (b)).[31] Organocatalytic approaches have also been established whereby a hydrogen-bonding donor in the presence of a halonium source results in enantioselective halocyclizations of *N*-allyl amides (NAAs, Scheme 1 (c)).[32–37]

Scheme 1. Known approaches for the synthesis of 5-oxazolines.



A more general approach for the cyclization of NAAs involves their treatment with a chiral hypervalent iodine compound. This induces an oxidative cyclization via a π-complexed iodane **A** similar to halonium sources (Scheme 2). The emerging alkyl-substituted iodane **B** is highly reactive and can be quenched by external nucleophiles (**Nu-H**) to generate highly substituted 5-oxazolines. A chiral aryl iodide is formed, which can be re-oxidized using an external oxidant.[38–51] This general method has been applied by Moran and co-workers using a well-established resorcinol-based chiral iodoarene catalyst,[52 53 53–57] but unfortunately with only modest results, in particular regarding stereoselectivity and substrate scope, with a focus on 6-membered *N*-heterocycles.[24]

Scheme 2. General mechanism for an iodane-mediated *N*-oxidative cyclization of NAAs.



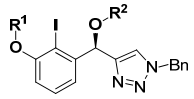
Our group recently established chiral triazole-substituted iodoarenes **1** and applied them in a wide range of enantioselective oxidative transformations (Figure 2).[49,50,58] In this article we want to report their further application to the as-yet underexplored oxidative cyclization of *N*-allyl amides.

We started our investigations using *N*-allyl benzamide, **2a**, as the model substrate (Table 1). It was established in our early studies that an additional substituent ortho to the central iodine atom is crucial for high reactivity and stereoselectivity in reactions performed with these catalysts. Therefore, we started with the *o*-OMe-substituted iodoarene catalyst **1a**, the most successful to be used so far. During a preliminary optimization we had already established acetonitrile as the best solvent for this reaction, in combination with selectfluor as a co-oxidant and TFA as an acid additive. While using catalyst **1a**, the 5-substituted oxazoline **3a** was isolated with a 67% yield and 85% ee.

We then systematically investigated the influence of both ether substituents (R^1 and R^2) in catalysts **1** on the reaction performance. Switching the TIPS group to other alkyl groups, such as catalysts **1b-1e**, was found to be counterproductive and resulted in diminished enantioselectivities (See entries 2-5). We also varied the alkyl ether at R^1 and decided to introduce greater sterical bulk at this position. With R^2 being TIPS again, replacement of the methyl with an ethyl ether for R^1 (catalyst **1f**) resulted in a small but less than significant improvement of the enantioselectivity.

Introduction of an isopropyl group (catalyst **1i**) resulted in by far the most significant improvements, as **3a** was now isolated with a 91% yield and 93% ee. By contrast, the corresponding use of benzyl ether (**1j**) or benzoyl ester (**1k**) was less effective (See entries 10 and 11).

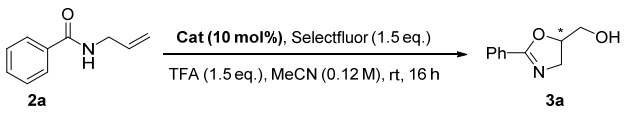
Figure 2. Structure of the chiral triazole catalysts **1**.



1

1a: R^1= Me, R_2= TIPS
1b: R^1= Me, R_2= Bn
1c: R^1= Me, R_2= Me
1d: R^1= Et, R_2= Me
1e: R^1= Et, R_2= Bn
1f: R^1= Et, R_2= TIPS
1g: R^1= *i*Pr, R_2= Me
1h: R^1= *i*Pr, R_2= Bn
1i: R^1= *i*Pr, R_2= TIPS
1j: R^1= Bn, R_2= TIPS
1k: R^1= Bz, R_2= TIPS

Table 1. Optimization of the Reaction Conditions.



2a **3a**

Entry[a]	Catalyst	Yield [%]	ee [%]
1	1a	67	85
2	1b	61	74
3	1c	62	64
4	1d	72	67
5	1e	71	74
6	1f	75	87
7	1g	83	70
8	1h	81	85
9	**1i**	**91**	**93**
10	1j	68	84
11	1k	80	84
12[b]	1i	65	93
13[c]	1i	48	92

[a] Reaction conditions: **2a** (0.40 mmol, 1.00 eq.), cat (0.04 mmol, 10 mol%), TFA (0.60 mmol, 1.50 eq.), selectfluor (0.40 mmol, 1.00 eq.), CH_3CN (0.12 M). [b] 5 mol% of 3h was used. [c] The reaction was performed at 0 °C and took 36 hours with 70% conversion of **2a**.

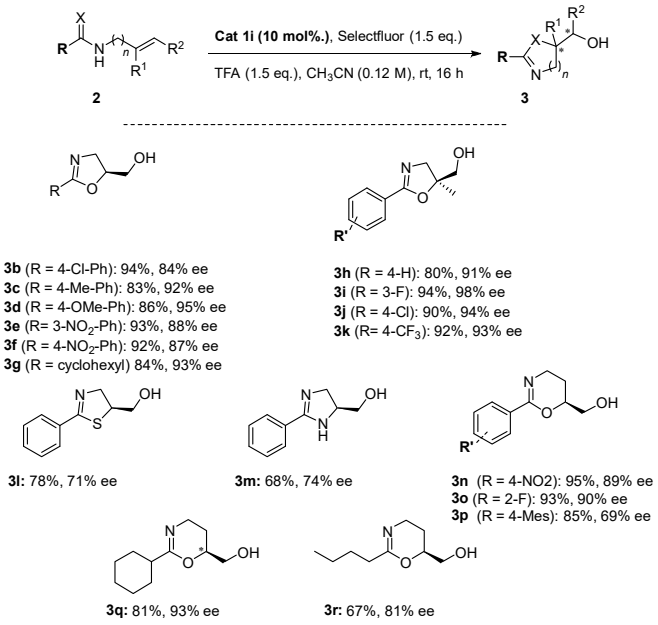
Decreasing the catalyst loading to 5 mol% had a negative effect on the yield. Reduction of the reaction time or performing the reaction at 0 °C did not improve the enantioselectivity but only led to lower reaction rates and incomplete conversions (See entries 12-13).

With the optimized conditions in hand, we elaborated the substrate scope of the oxidative cyclization (Scheme 3). The NAA derivatives **2b–f**, with additional substituents at the 2-aryl group, provided the corresponding oxazolines **3b-f** in

yields and enantioselectivities comparable to the parent compound **3a** (84-92%), regardless of the electronic nature of the substituent. Comparison of the rotary power of the 4-nitro derivative **3f** with a known literature value allowed us to determine the absolute configuration of the products to be (S).[59] Cyclic aliphatic substituents (R^1 = cyclohexyl) were tolerated as well, giving **3g** with a 84% yield and 93% ee.

Next, we wondered whether quaternary stereocenters could be constructed.[60–63] We therefore decided to apply our method for the synthesis of quaternary 2-oxazolines starting from various *N*-(but-3-en-2-yl) benzamides **2h-2k** (R^1 = Me, R^2 = H). The desired products **3h-3k** could be observed in high yields of up to 94% and excellent enantioselectivities (91-98% ee). The enantioenriched thiazoline **3l** and the imidazoline **3m** were prepared for the first time by this method, although yields and enantioselectivities were significantly lower in direct comparison with their oxa derivatives (71% ee and 74% ee). It is nonetheless worth mentioning that these *N*-heterocycles are very important core structural motifs found in many biologically active compounds and this method provides a so-far undescribed means of accessing them.[64–67]

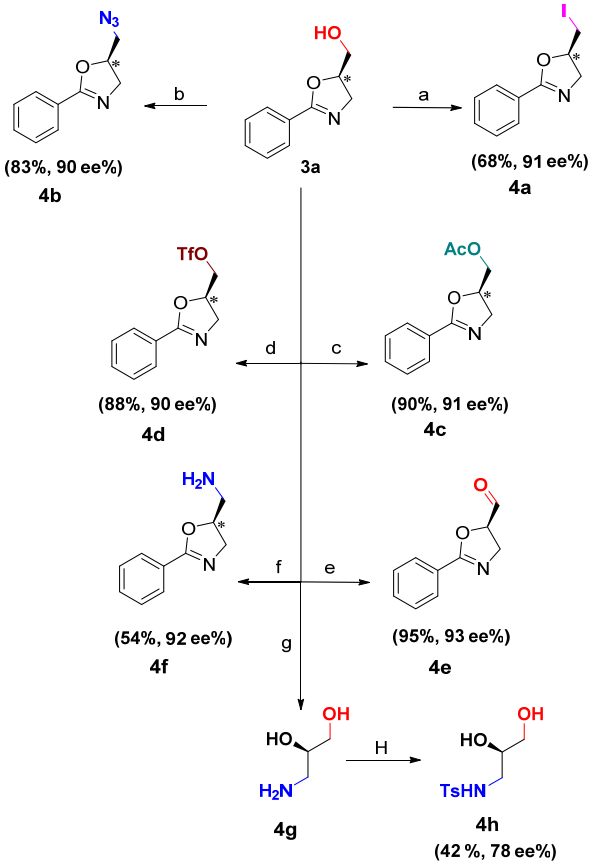
Scheme 3. Substrate Scope



We subsequently focused on the synthesis of 6-membered *N*-heterocycles. Application of *N*-homoallyl benzamide **2n** and **2o** (n = 2) provided the oxazines **3n** and **3o** in yields of 95% and 93% and enantioselectivities of 89% ee and 90% ee, respectively. The mesityl-substituted derivative gave the corresponding oxazine **3p** in comparable yields but with a diminished enantioselectivity (69% ee).

Aliphatic homoallyl amides **2q** and **2r** were subsequently investigated, giving the desired 2-cyclohexyl- and 2-*n*-butyl-substituted derivatives **3q** and **3r** in respective yields of 81% and 67% and enantioselectivities of 93% and 81% ee for each. Applications of similar compounds have been reported for the preparation of poly(2-oxazoline) gels for delayed drug delivery systems.[68] Again, our method provides unique access to these enantioenriched *N*-heterocycles.

Scheme 4. Derivatization of Oxazoline **5a**.



Reaction conditions: a) I_2 (1.20 eq.), PPh_3 (1.30 eq.), Pyridine (0.95 M), rt, 24 h. b) NaN_3 (3.00 eq.), $BF_3.Et_2O$ (1.50 eq.) Dioxane, rt, 24 h. c) Acetic anhydride (2.00 eq.) DCM, rt, 4 h. d) TF_2O (1.20 eq.), Pyridine (1.10 eq.), DCM, rt, 16 h. e) MnO_2 (12.0 eq.), $CHCl_3$, 60 °C. 4 h. f) Pthalimide (1.10 eq.), PPh_3 (1.10 eq.) DIAD (1.30 eq.), Hydrazine (1.50 eq.), THF (0.42 M), 80 °C, 8 h. g) 1-$NaBH_4$ (1.20 eq.), I_2 (1.00 eq.), 2- HCl in MeOH, 24 h. h) TsCl (1.20 eq.) MeCN, rt, 6 h.

Since 5-oxazolines are potentially useful intermediates for the synthesis of other chiral building blocks, we finally elaborated further synthetic transformations of **3a** (Scheme 4). The OH group could be replaced by iodine under Mitsunobu conditions to afford **4a** in 68% yield without a significant loss of enantiomeric excess.[69] Azidation was achieved using a method devised by Kumar and co-workers, treating **3a** with NaN_3 and BF_3Et_2O to give **4b** in 83% yield and 91% ee.[70] Protection of the OH group to the corresponding acetates and triflates (**4c** and **4d**) was successful as well. In addition, the corresponding aldehyde could be obtained by treatment of **3a** with MnO_2, to give **4e** in 95% yield and 93% ee. Interestingly, no overoxidation of the oxazoline was observed. A Mitsunobu reaction was also utilized to prepare the primary amine **4f** in a moderate yield (54%) but

sustaining the stereochemistry (92% ee).[71] Lastly, we prepared 3-aminopropane-1,2-diol by a reduction of **3a** followed by acid-mediated ring-opening to give the amino diol **4g**. Since this compound could not be analyzed by HPLC, it was directly transformed into the *N*-tosylated derivative **4h**. **4h** was isolated in 42% yield but with a diminished selectivity of 78% ee

In summary, we have established a practical method for the enantioselective oxidative cyclization of *N*-allyl amides by using an improved triazole-substituted iodoarene catalyst. This method is characterized by a broad substrate scope which allows the construction of highly enantioenriched 5-oxazolines, thiazolines, and imidazolines. Quaternary stereocenters can be constructed with high efficiency as well and the method was further extended to oxazines. Many of the constructed compounds can serve as chiral building blocks for the synthesis of interesting chiral target structures. This was demonstrated in a variety of further functionalizations, in particular of the terminal OH group.

In further investigations, we aim to apply C1-symmetric triazole-based iodoarenes in similar oxidative cyclizations to generate other useful 5- and 6-membered heterocycles. Additionally, cascade reactions in which the reactive hypervalent iodine intermediate is trapped directly by nucleophiles other than OH will also be part of future investigations.

ASSOCIATED CONTENT

Supporting Information. All supporting information is available free of charge on the ACS Publications website at DOI: XXX. This includes all experimental procedures and characterization data.

AUTHOR INFORMATION

Author Contributions

The manuscript was written by Boris J. Nachtsheim and Ayham H. Abazid. Ayham H. Abazid and Tom-Niklas-Hollwedel performed the experiments. All authors have given approval to the final version of the manuscript.

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Funding Sources

This work is supported by the DFG (Deutsche Forschungsgemeinschaft – Grant NA 955/3-1).

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Ayham H. Abazid acknowledges the Scholars at Risk organization for personal funding.

ABBREVIATIONS

PPh_3: Triphenylphosphine; BF_3Et_2O: Boron trifluoride diethyl etherate; DCM: Dichloromethane; DIAD: Diisopropyl azodicarboxylate

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