

A Catalytic Highly Enantioselective Synthesis of Spirooxazolines

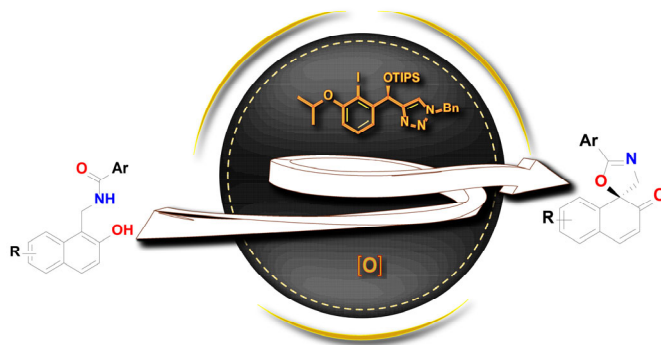
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Supporting Information Placeholder

ABSTRACT: A catalytic highly enantioselective synthesis of spirooxazolines is presented. Starting from readily available 2-naphthol-substituted benzamides and using catalytic amounts of a chiral triazole-substituted iodoarene catalyst, a variety of spirooxazolines can be isolated through an enantioselective oxidative dearomatization in up to 92% yield and 97% ee. The further synthetic utility of the optically enriched spirooxazolines was examined providing a corresponding 2-naphthalenone and an oxepin.



Spirocycles are well represented in many natural products and commercial drugs.¹ These unique molecular scaffolds have the advantage of providing stiff three-dimensional arrangements based on the tetrahedral nature of the spirocarbon. This allows enzyme pocket binding in a highly specific manner in terms of H-bonding, hydrophobic,² and π -stacking interactions.³ While spirocycles can be found in abundance in natural products, they are only rarely found in pure synthetic pharmacophores due to their difficult enantioselective synthesis. A particular underrepresented class of synthetic spirocycles are spiro(is)oxazolines, although they can be found in a variety of natural products such as Agelolin A and B (**1a** and **1b**), isolated from marine sponges of the genus *Agelas*,⁴ or Calafianin **2** from the sponge *Aplysina gerardogreeni*.⁵ The oxazoline derivatives **3** were extracted from the plant *Gemmingia chinensis* (Figure 1).⁶

The benefits of spirooxazolines as a unique class of spirocyclic compounds and their potential as highly variable scaffolds in medicinal chemistry and material science are encouraging chemists to develop new strategies for their synthesis. Synthetic strategies of spirocycles in general have been reported based on radical cyclizations,⁷ rearrangements,⁸ oxidative or reductive coupling reactions⁹ and cycloadditions.¹⁰

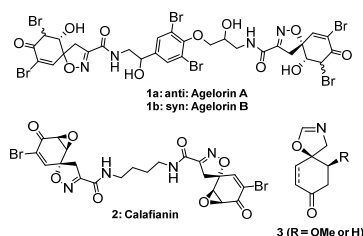


Figure 1. Examples of natural products containing spirooxazoline.

Metal-catalyzed reactions such as the metathesis reaction, the Heck- and the Pauson–Khand reaction¹¹ as well as the Nazarov-cyclization¹² have been applied for the *de novo*

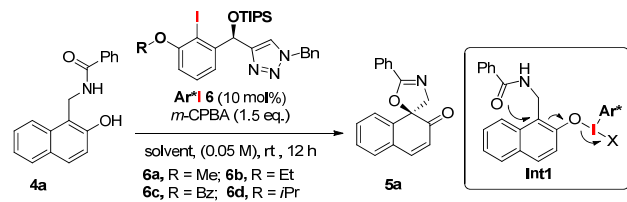
synthesis of spirocyclic scaffolds. A variety of spirocyclic natural-products have been synthesized by metal-catalyzed approaches, such as (–)-vitrenal,¹³ (+)-majusculone,¹⁴ and α -acoradiene.¹⁵ Another important approach for the synthesis of spirocycles is the intramolecular oxidative dearomatization of phenol and naphthol derivatives which can be efficiently accomplished through the application of hypervalent iodine reagents.^{16,17} The first report for such a reaction was in 1998, when Ciufolini *et al.* reported the oxidative cyclization of tyrosine to form spirolactams, mediated by (diacetoxyiodo)benzene (PIDA) in moderate yields.¹⁸ Many variants followed.¹⁹

Enantioselective spirocyclizations, with the Kita-spirocyclization being the most prominent example, have been developed with great success as well.^{20,21} In this regard, spirooxazolines have been widely neglected as target structures for oxidative cyclizations.²² Recently, Moran and co-workers determined a new method for synthesizing spirooxazolines through the oxidative cyclization of phenols containing pendent amides mediated by iodine(III). In this seminal report, they also applied this reaction to 2-naphthol using chiral urea-derived iodoarenes, unfortunately with only modest results. In particular the stereoinduction was moderate with 14% ee in the best case.²³

Our group recently developed chiral triazole-substituted iodoarenes, and successfully applied these chiral C1-symmetric iodoarene catalysts in a plethora of oxidative enantioselective transformations such as α -oxytosylations, (spiro)lactonizations, rearrangements and benzylic hydroxylations.^{21,24} Intrigued by their high reactivity, we wondered whether these omnipotent catalysts can be applied in the yet underexplored generation of spirooxazolines through an oxidative spirocyclization of suitable substrates. We started our investigations using *N*-((2-hydroxynaphthalen-1-yl)methyl)benzamide **4a** as the model compound (Table 1). Oxidative spirocyclization of **4a** by a dearomatizing oxidative C–O-bond connection between the amides carbonyl oxygen and C1 of the 2-naphthol unit as shown in **Int1** should give spirocyclic 2-naphthalenone **5a**.

We initially investigated four successful catalysts (**6a-d**) from our recent work (entries 1-4).²⁵ It was found that catalyst **6d** showed the highest reactivity and selectivity for the desired product **5a** (entry 4). While ethyl acetate and pure HFIP as well as MeOH/MeCN mixtures did not improve yields and selectivities (entries 5-7), a further optimization of the reaction conditions revealed a mixture of acetonitrile and HFIP to be a highly effective solvent system (entry 8). Performing the reaction at 0 °C finally improved the stereoselectivity of product **5a** slightly to 96% ee (entry 9). The absolute configuration of **5a** was proven by comparison between a calculated CD-spectrum and the observed spectrum (see ESI, Figure S-1).

Table 1. Optimization of the reaction conditions.

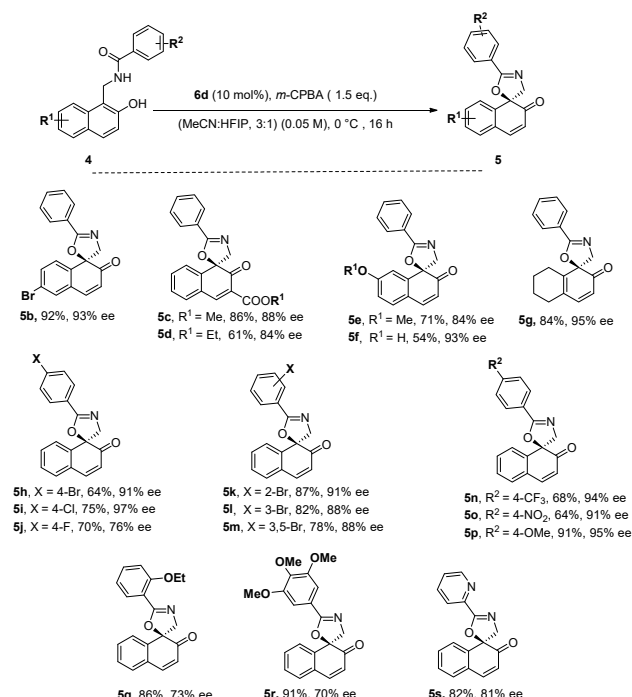


Entry ^[a]	Catalyst	Solvent	Yield [%]	ee [%]
1	6a	MeCN	60	67
2	6b	MeCN	68	74
3	6c	MeCN	63	78
4	6d	MeCN	76	85
5	6d	EtOAc	71	64
6	6d	HFIP	72	76
7 ^[b]	6d	MeCN:MeOH	68	72
8 ^[b]	6d	MeCN:HFIP	80	90
9 ^[b, c]	6d	MeCN:HFIP	81	96

[a] Reaction conditions: **4a** (0.15 mmol, 1.00 eq.), cat (0.015 mmol, 10 mol%), *m*-CPBA (0.23 mmol, 1.50 eq.), solvent (0.05 M). [b] Ratio of 3:1. [c] Reaction performed at 0 °C for 16 h for full conversion of **4a**.

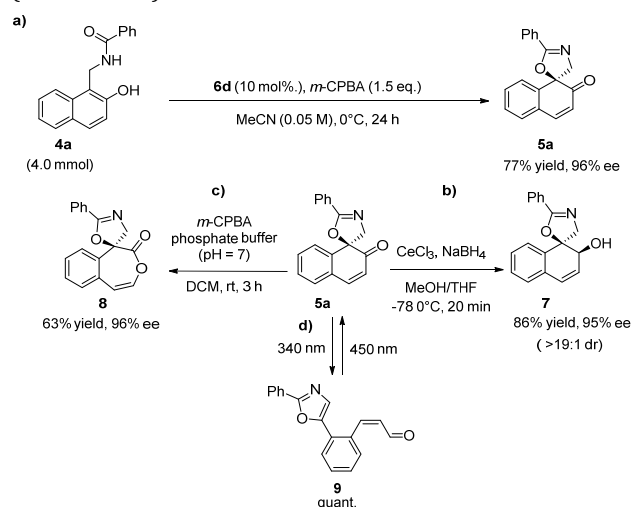
Under these optimized conditions, the applicable substrate scope was examined (Scheme 2). Initially, we introduced diverse substituents on the 2-naphthol ring. Halogen-substituents are well tolerated for example giving the 6-bromo derivative **5b** in 92% yield and 93% ee. 3-Carboxy-alkylesters gave spirooxazolines **5c** and **5d** in up to 86% yield and 88% ee. 7-Methoxy- and hydroxyderivatives as electron rich examples can also be submitted to the spirocyclization giving **5e** and **5f** with good results. Even though the latter was isolated in high enantioselectivity (93% ee), yield significantly dropped to 54%, possibly due to undesired oxidations of the phenol. A hexahydro 2-naphthalenone can be transformed into target compound **5g** in 84% and 95% ee. Next, we varied the substitution pattern of the aryl amide. Introduction of halogen substituents yielded target compounds **5h-m** with good yields of 64–87%, and enantioselectivities of up to 97% for the 4-chloro derivative **5i**. The presence of strongly electron-withdrawing trifluoromethyl or nitro groups was tolerated as well in the

cyclization, resulting in formation of **5n** and **5o** in good yields and excellent enantioselectivities of up to 94% ee. Methoxy- and ethoxy-substituted arenes **4p** and **4q** gave spirooxazolines **5p** and **5q** in high yields of 91% and 86%, respectively, with an excellent enantioselectivity for **5p** of 95% ee and a moderate enantioselectivity of 73% ee for **5q**. A highly electron rich trimethoxy-substituted derivative yielded the corresponding spirooxazoline **5r** in high yield, but with a diminished enantioselectivity of 70% ee. A 2'-pyridine-substituted amide was also tolerated in this cyclization, forming the corresponding spirooxazoline **5s** with 82% yield and 81% ee.



Scheme 2. Substrate scope.

To prove the synthetic robustness of our method, a large-scale synthesis was performed, giving spirooxazoline **5a** in constant yield and enantioselectivity on a 4 mmol scale. (Scheme 3 - a).



Scheme 3. Synthetic applicability.

The further synthetic utility of the optically enriched spirooxazolines was also investigated. A diastereoselective Luche reduction of **5a** yielded the C2-spirocyclic tetrahydronaphthalenole **7**, with almost the same enantiopurity (Scheme 3 - b).²⁶ By addition of *m*-CPBA **5a** was oxidized through a Baeyer-Villiger oxidation to the oxepin **8**, again with excellent retention of the stereocenter (Scheme 3-c). Interestingly, this reaction was not observed during our previous investigations as a potential side reaction.

Spiropyrans and spirooxazines received attention in material science due their reversible photoresponsive properties.²⁷ Industrial applications of spirooxazines include photoresponsive sunglasses and ophthalmic lenses.²⁸ In this regard, the closed form **5a** could potentially undergo ring opening after photoactivation, either by heterolytic cleavage of the C(spiro)–O bond or electrocyclization, to give the open form, which absorbs at a longer wavelength due to an extended π -system.²⁹ We used 340 nm light for the photoisomerization reaction of spirooxazoline **5a** to construct the open form **9**, which has a yellowish color. The aldehyde **9** absorbed light at 450 nm to revert to the closed form **5a** as the racemate (Scheme 3 - d). This is a rare case of a switchable optical active spirooxazine and further applications in chiral optical devices are under current investigations.

In conclusion, we herein present the first highly enantioselective oxidative spirocyclization of amide-substituted 2-naphthols using chiral hypervalent iodine catalysis. This method provides a variety of enantioenriched spirooxazolines in remarkable yields and enantioselectivities. The reaction is compatible with a wide variety of substrates, including electron-rich and electron-poor naphthalene benzamides as well as *N*-heterocycles. The further synthetic utility of these compounds allows the preparation of two interesting derivatives by a diastereoselective 1,2-reduction of the 2-naphthalenone and ring-enlargement through a Baeyer-Villiger oxidation. Finally, the principle photo-switchable properties of the so observed chiral spirooxazoline is demonstrated.

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.

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Author Contributions

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

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

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

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