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Noncovalent Organocatalysis: A Powerful Tool for the Nucleophilic Epoxidation of α-Ylideneoxindoles

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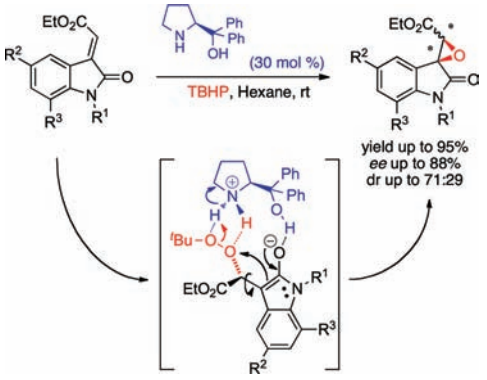
ABSTRACT



A novel asymmetric nucleophilic epoxidation for α-ylideneoxindole esters has been successfully devised, resulting in enantioenriched spiro compounds with two new contiguous stereocenters. The employed (*S*)-α,α-diphenylprolinol functions as a bifunctional catalyst, creating a complex H-bond network in conjunction with a substrate and an oxidant.

As a consequence of their functional group diversity and complex architectural platforms, synthetic and natural oxindole products have drawn the attention of an increasing number of chemists.[1] Their wide range of biocidal properties have also piqued curiosity in medical fields.[2] Specifically, spiro-epoxyoxindoles and their closest derivatives, 3-substituted 3-hydroxyoxindoles, have been found to possess remarkable medicinal effectiveness and serve a unique role in direct access to highly valuable bioactive molecules.[3] Noteworthy examples are some benzoyl-substituted oxiranes, which have been tested as antitubercular agents,[4]

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and convolutamydines A–E, which are potent inhibitors of the differentiation of promyelocytic leukemia cells.[5] Although several elegant strategies have been reported for 3-hydroxyoxindoles,[6] the current synthetic repertoire to a spiro[oxirane-oxindole] framework still suffers from poor stereocontrol, employs metal catalysis, and displays a poor substrate scope.[7]

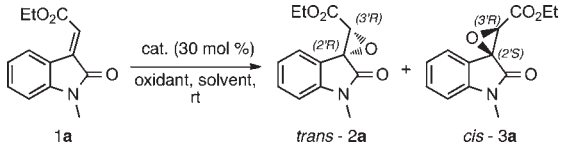
Encouraged by the previously observed high reactivity of 3-(oxyphosphonylmethylene)oxindoles with nucleophilic oxidants,[8] we devised the possibility of synthesizing optically active spiro-epoxyoxindole esters by exploiting an asymmetric catalytic modification of the Weitz–Scheffer epoxidation[9] of electron-poor α-ylideneoxindoles (**1**). Aside from the well-established Juliá–Colonna reaction[10] and the phase transfer catalysis approach,[11] efficient systems have been devised for the asymmetric epoxidation of α,β-unsaturated aldehydes and ketones. Among the former class of substrates, excellent results have been obtained by employing diarylprolinol silyl ethers,[12] chiral phosphoric amine salts,[13] and diphenylfluoromethylpyrrolidine as highly effective catalysts.[14] Diphenylprolinol[15] as well as guanidine[16] and amino alcohol based[17] catalysts are more efficiently involved in the asymmetric epoxidation of α,β-unsaturated ketones.

Conversely, the application of such organocatalytic strategies to α,β-unsaturated carboxylic acid derivatives is still a mostly unexplored field[18] and remains a challenging endeavor of great interest.

By taking advantage of the impressive progress with carbonyl derivatives, we pursued our research by investigating the organocatalytic epoxidation of α-ylideneoxindoles (**1**), which are electron-poor olefins bearing two electron-withdrawing groups on the opposite sides of the double bond. Here, we report the initial successful asymmetric oxidation to form the spiro[oxirane-oxindole] derivatives **2** and **3** promoted by α,α-diaryl-prolinol derivatives as bifunctional catalysts (Table 1).

Because a number of chiral secondary amines exhibit different outcomes when employed as catalysts, the enantiopure prolinol derivatives **A**–**E** (Figure 1) were initially used as organocatalysts (30 mol %) to promote the asymmetric epoxidation of a model electron-poor olefin, *N*-methyl-α-ylideneoxindole **1a** (Table 1).

Table 1. Effects of the Organocatalyst and Solvent during Epoxidation Reactions[a]



entry	cat	solvent	mL	time (h)	yield (%)[b]	dr[c] **2a**:**3a**	**2a** *ee* (%)[d]	**3a** *ee* (%)[d]
1	**A**	Hexane	1.3	72	94	64:36	70	22
2	**B**	Hexane	1.3	40	83	25:75	37	2
3	**C**	Hexane	1.3	140	95	36:64	58	1
4	**D**	Hexane	1.3	360	75	66:34	38	22
5	**E**	Hexane	1.3	80	89	64:36	72	36
6[e]	**A**	Hexane	1.3	36	84	96:4	2	1
7[f]	**A**	Hexane	1.3	400	80	66:34	70	22
8	**A**	Hexane	0.5	12	96	68:32	45	14
9	**A**	Hexane	1.0	48	95	67:33	67	20
10	**A**	Hexane	2.0	68	87	64:36	74	26
11	**A**	Hexane	2.7	72	95	64:36	82	19
12[g]	**A**	Hexane	2.7	72	92	66:34	64	36
13	**A**	Hexane	4.0	120	90	55:45	80	25
14	**A**	$CHCl_3$	0.6	240	55	66:34	71	16
15	**A**	CH_3CN	0.6	192	90	68:32	46	40
16	**A**	EtOH	1.3	192	70	61:39	48	39
17	**A**	DMSO	1.3	96	83	78:22	33	40
18	**A**	THF	0.6	192	85	68:32	57	29
19	**A**	Toluene	0.6	120	73	59:41	69	18

[a] Unless otherwise stated, the reaction conditions were as follows: *N*-methyl-α-ylideneoxindole **1a** (0.5 mmol), TBHP (0.6 mmol), catalyst (0.15 mmol), and solvent at rt. [b] The yields of the isolated products are expressed as the sum of the diastereomers. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. [e] H_2O_2 (30% in water, 0.15 mmol) was employed as the oxidant. [f] Cumene hydroperoxide (CHP, 0.15 mmol) was employed as the oxidant. [g] The reaction was performed at 4 °C.

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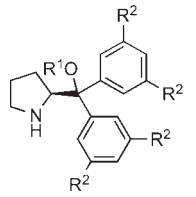


catalyst	R^1	R^2
A	H	H
B	CH_3	H
C	TMS	H
D	H	CF_3
E	H	CH_3

Figure 1. Organocatalysts examined in this study.

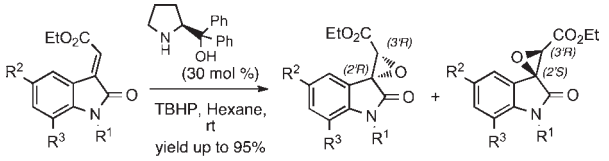
We selected *tert*-butylhydroperoxide (TBHP) as the oxidant and hexane as the solvent, even though both the substrate and products were barely soluble in such a medium. Despite the substrate having the *E* configuration, both spiro-oxirane-2-carboxylates (*trans*-**2a** and *cis*-**3a**) were always obtained, with the former as the major diastereoisomer.[19] The initial hypothesis of a fast interconversion between the two observed products was quickly excluded because independent experiments, performed by treating the *trans*-**2a** spiro-epoxide with the same catalyst/oxidant system, provided none of the corresponding *cis*-**3a** diastereomer.

Of the employed catalysts, the simplest α,α-diphenylprolinol (*S*)-**A** provided the *trans*-**2a** spiro-epoxide with good enantioselectivity (70% *ee*, entry 1), while either the *O*-methylated (*S*)-**B** (entry 2) or the more hindered *O*-trimethylsilylated (*S*)-**C** (entry 3) provided decreased enantiomeric excess and an inverted diastereomeric ratio. Such results strongly suggested the key role of the free OH group in the catalyst as establishing an H-bond network with both the substrate and reagent. Despite this evidence, the introduction of EWGs on both catalyst aromatic rings [Ar = 3,5-$(CF_3)_2$-C_6H_3, (*S*)-**D**], which should have promoted H-bond formation, only protracted the reaction time without increasing the overall enantioselectivity (entry 4). However, similar steric hindrance on the aryl groups [Ar = 3,5-$(CH_3)_2$-C_6H_3, (*S*)-**E**] led to analogous yield and stereoselectivity results (entry 5) with the first employed catalyst (*S*)-**A**. On the basis of these preliminary trials, subsequent reaction optimization was performed with the less expensive α,α-diphenylprolinol (*S*)-**A**, which, surprisingly, provided the optimal enantioselectivity when more hexane was added (entry 11). Additional screening of oxidizing agents (H_2O_2 in entry 6 and CHP in entry 7), temperature (entry 12), and solvents (entries 14–19) failed to improve either the yield or the stereoselectivity and resulted in a longer reaction time and poorer substrate conversion.

The given stereochemical assignments are based on a thorough comparison of the reported experiments, analytical data, and a quantum mechanical *ab initio* calculation of chiroptical properties.[19] Indeed, once it is unambiguously determined via ^{1}H NMR and NOESY experiments,[15] the *trans*/*cis* configuration of the obtained diastereomers (**2a** and **3a**) was used to simulate the optical rotation dispersion (ORD).[20] This calculation was performed using an arbitrarily fixed absolute configuration (2′*R*,3′*R*) for the major enantiomer of *trans*-**2a**. Because the sign, order of magnitude, and uniform trend of the experimental ORD were correctly reproduced by the calculations, (2′*R*,3′*R*)-**2a** was strongly supported as the absolute configuration. The (2′*S*,3′*R*) configuration was assigned to the major enantiomer of *cis*-**3a** by applying the same quantum mechanical approach.

The developed conditions were evaluated using the analogous α-ylideneoxindoles **1b**–**m**, which were variously substituted on both nitrogen (R^1) and the aromatic ring (R^2 and R^3). These results are summarized in Table 2. The presence of a halide in position 5 (**1b**, **1c**) or 7 (**1e**–**g**) induced a surprising inversion in *dr* with respect to the model reaction, whereas the enantioselectivity was almost the same or even better with bromine in position 7 (88% *ee*, *trans*-**2g**). Similar stereoselectivity was observed when the substrate bearing the CF_3O group was employed (**1d**). Conversely, the initial *dr* (in favor of *trans* diastereomers) was slowly restored by removing the decoration on the fused aromatic ring and diversifying the substituent on the nitrogen atom (**1h**, **1i**, **1m**). However, a decrease in the enantioselectivity was observed. Additional structural and electronic modifications on both aromatic moieties (**1j**–**l**) resulted in the optimal diastereomeric excess without improving the enantioselectivity.

Table 2. Substrate Scope of the Asymmetric Epoxidation Reactions of the 3-Ylideneoxindoles **1a**–**m**[a]



1a-m *trans* - **2a-m** *cis* - **3a-m**

	R^1	R^2	R^3	time (h)	yield (%)[b]	dr (**2**:**3**)[c]	**2** *ee* (%)[d]	**3** *ee* (%)[d]
1a	CH_3	H	H	72	95	64:36	82	19
1b	CH_3	F	H	30	75	48:52	84	30
1c	CH_3	Cl	H	42	92	40:60	76	42
1d	CH_3	CF_3O	H	48	70	40:60	78	30
1e	CH_3	H	F	36	85	34:66	80	27
1f	CH_3	H	Cl	38	88	25:75	81	32
1g	CH_3	H	Br	48	71	30:70	88	58
1h	Ph	H	H	48	80	54:46	74	12
1i	Bn	H	H	48	92	66:34	56	20
1j	Bn	^{i}Pr	H	192	89	71:29	62	26
1k	Bn	CH_3O	H	192	80	70:30	52	16
1l	3-NO_2Bn	CH_3O	H	190	88	70:30	78	20
1m	2,4-Cl_2Bn	H	H	96	80	56:44	60	20

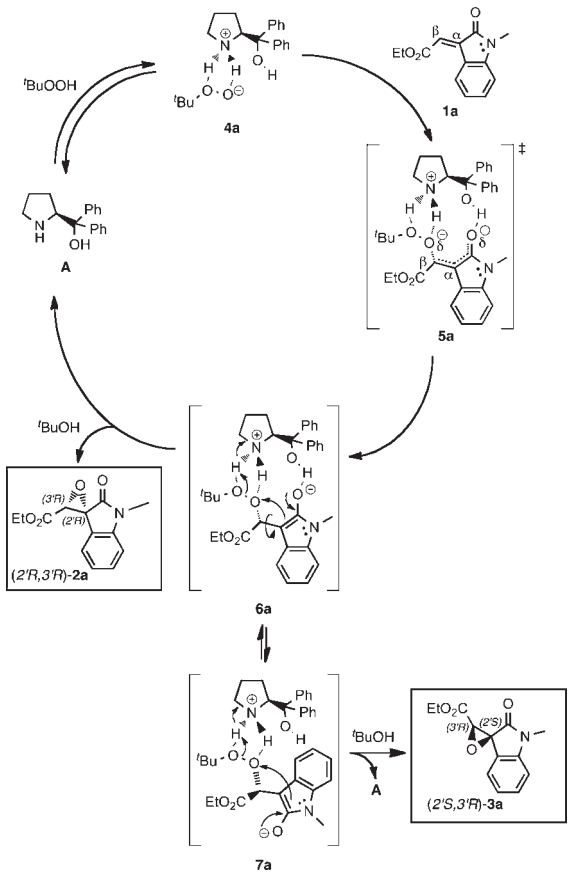
[a] Reaction conditions: α-ylideneoxindole **1** (0.5 mmol), catalyst **A** (0.15 mmol), TBHP (0.6 mmol) and HPLC-grade hexane (2.7 mL) at rt. [b] The yields of the isolated products are expressed as the sum of the diastereomers. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis.

The experimental evidence and the obtained configuration (2′*R*,3′*R*) of the major stereoisomer could be explained

(19) Spectroscopic analyses of **2a** and **3a**, ORD values, and the complete calculated/experimental data discussion are reported in the Supporting Information.

by assuming the catalytic cycle depicted in Scheme 1, which fully agrees with the recent statements regarding the asymmetric epoxidation of α,β-unsaturated ketones.[15b] According to this hypothesis, we propose the following: (*i*) the interaction between TBHP and the catalyst activates the oxidizing agent, leading to the tight ion pair **4a**; (*ii*) the first regiospecific attack of **4a** at the C_β carbon[21] of the substrate is promoted by both the intermediate aromatization and formation of a stabilizing H-bond between the OH catalyst and the partial negative charge on the lactam carbonyl moiety; (*iii*) thus, the reagent approach is preferentially driven toward the less-hindered *Re*-face of the double bond, resulting in the aromatic and long-living **6a** intermediate; and (*iv*) two alternative evolutions of **6a** may result in either the oxirane (2′*R*,3′*R*)-**2a** (via irreversible direct ring closure) or the diastereomer (2′*S*,3′*R*)-**3a** (*via* intramolecular H-bond breaking and the rapid subsequent rotation around the $C_\alpha-C_\beta$ σ-bond to produce the **7a** intermediate).

Scheme 1. Postulated Reaction Mechanism



This catalytic pathway also accounts for the poor enantioselectivity observed for the *cis*-**2a** diastereomer (Table 1), which is a consequence of both the less-favored *Si*-face attack and the continuous interconversion between the aromatic intermediates (**6a** and **7a**). Such an equilibrium is shifted toward intermediate **7** when the presence of halides on the fused aromatic ring facilitates the formation of an additional stabilizing H-bond between the substrate and OH catalyst (Figure 2).

The successful achievement of the desired spiro compounds provides a novel, nucleophilic approach to the organocatalytic epoxidation of α,β-unsaturated carboxylic acid derivatives. This route offers a valuable alternative to the electrophilic procedure developed by Shi.[22] Additionally, it confirmed the action of noncovalent catalysis that relies on a hydrogen bond network between the substrate and the bifunctional catalyst/oxidant system.

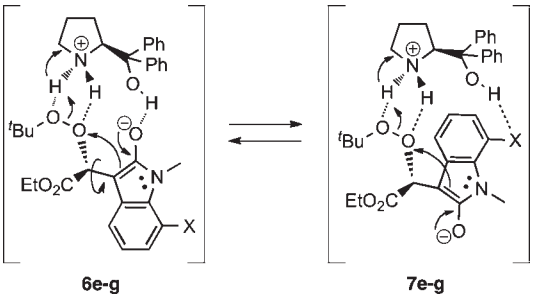


Figure 2. Interconversion between the **6e**–**g** and **7e**–**g** intermediates (X = F, Cl, or Br).

Detailed studies to elucidate the mechanism and broaden the substrate scope are ongoing in our laboratories and will be reported in due course. Finally, these results provide straightforward access to new spirocyclic oxindolic oxiranes, which are extremely attractive building blocks and intermediates due to the presence of additional moieties that are capable of additional chemical elaboration.

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Supporting Information Available. Detailed experimental procedures and a full characterization and copies of the ^1H, ^{13}C NMR spectra, HPLC, and ORD calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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