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Quinine as an organocatalytic dual activator for the diastereoselective synthesis of spiro-epoxyoxindoles

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ABSTRACT

A highly efficient organocatalytic approach has been developed for the diastereoselective epoxidation of (*E*)-3-ylidene-indolin-2-one derivatives using readily available natural product quinine and urea-hydrogen peroxide (UHP) in DCM at 10 °C to afford *trans* spiro-epoxyoxindoles which were further utilized to obtain *β*-hydroxy-*α*-amino esters by water mediated regioselective ring opening from the less hindered end with aniline derivatives, under sonication.

Oxindoles are widely found in nature and have demonstrated diverse biological properties.[1] The activity mainly resides in the substitution at the C-3 quaternary centre. In particular, benzoylated spiro-epoxyoxindole[2] and its 1,2-diol derivative (TMC-95A)[3] have demonstrated remarkable antifungal, antitubercular and anticancer activities (Fig. 1). The unique structural feature and diverse pharmacological spectrum of this scaffold has attracted the efforts of researchers to synthesize these molecules in an efficient[4] and stereoselective[5] manner. The available methods for the stereoselective synthesis of the target molecule involve either direct reaction on isatins such as Darzen type condensation via in situ generation of ylide[5a–g] or organocatalytic[5f] epoxidation reaction of α-ylideneoxindole derivatives. However, the drawbacks associated with these strategies such as use of an L-proline based organocatalyst synthesized in 4–5 steps, high catalyst loading and long reaction time with moderate stereoselectivity demands robust and economic methods for the synthesis of these bioactive molecules. Based on our interests in asymmetric synthesis[6] and reaction methodology,[7] we developed a catalytic epoxidation protocol for α-ylideneoxindoles using the readily available natural product quinine as organocatalyst and urea-hydrogen peroxide as oxidant. The α-ylideneoxindoles required for the studies were synthesized by Horner–Wadsworth–Emmons (HWE) reaction on *N*-alkylated isatin derivatives to afford the desired *trans* alkenes in good yield (Scheme 1).[5f]

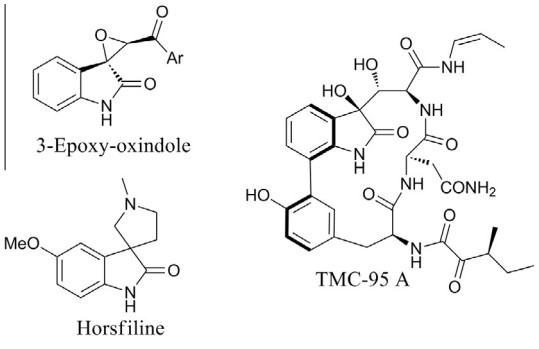
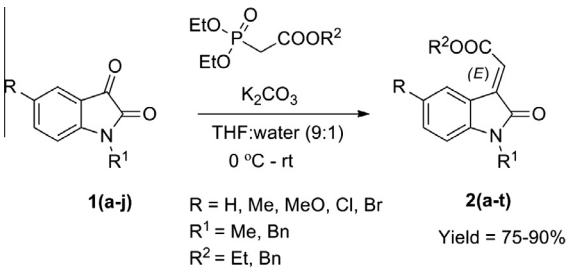


Figure 1. A few bioactive 3-substituted-oxindoles.



Scheme 1. Synthesis of (*E*)-3-ylidene-indolin-2-one derivatives.

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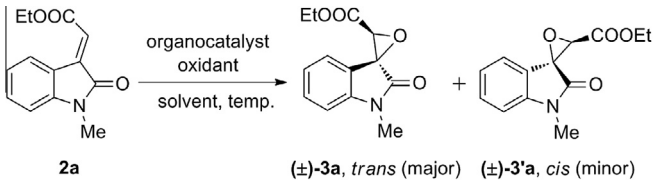


Scheme 2. Organocatalytic synthesis of 3-spiro-epoxyoxindole.

Epoxidation of (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (**2a**) was attempted with natural and synthetic chiral organocatalysts such as L-proline (catalyst A), *N*-allyl-L-prolinol[8a] (catalyst B), (*S*)-3-amino-4-methyl-*N*-phenylpentanamide[8b] (catalyst C) and quinine (catalyst D) in the presence of different peroxides as oxidant (Scheme 2). From the results obtained (Table 1), it could be inferred that catalysts A, B and C were inefficient and afforded only a trace amount of the desired product. On the other hand, reaction with 0.3 equiv of the catalyst D, quinine and 3.0 equiv of aq H_2O_2 in DCM as solvent at 25 °C afforded the desired product (**3a**) with poor yield (20%) and a moderate diastereomeric ratio of 80:20 as determined from the ^{1}H NMR spectra of the reaction mixture (Table 1, entry 4). Examination of the catalytic activity of quinine at lower loading demonstrated that only 0.1 equiv of quinine is sufficient for the reaction (Table 1, entry 9). Interestingly, in a separate study, while screening the different peroxides as oxidant with varying molar ratios, we observed that 2.0 equiv of urea–hydrogen peroxide facilitates the complete conversion of the starting material (Table 1, entries 7 and 8). In a control experiment performed with (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate and UHP in DCM without the addition of quinine, the reaction did not afford the product while the starting material remained as such even after 30 h (Table 1, entry 10). This clearly reveals the role of quinine not only in imparting stereoselectivity but also in catalyzing the reaction. Screening various solvents for the reaction indicated DCM to be the most suitable (Table 2). To evaluate the effect of temperature on the stereoselectivity of the reaction, a set of reactions were performed at low temperatures of 20 °C, 10 °C and 0 °C (Table 2, entries 6–8). The best result was obtained at 10 °C where the reaction afforded the spiro-epoxyoxindole with 94% yield and 98:02 *trans* diastereoselectivity. Surprisingly at 0 °C the reaction was sluggish and afforded only 50% of the product after 30 h. The *trans* selectivity of the reaction was confirmed by NOESY experiment of the major diastereomer (**3b**). No nuclear Overhauser effect was observed between the proton (H_e) attached to the oxirane ring and the aromatic proton (Ar–H_a) which clearly illustrates that the phenyl ring and H_e proton are *trans* to each other (Fig. 2).

Table 2
Effect of solvent and temperature[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	dr[c] (*trans*:*cis*)
1	THF	25	36	45	90:10
2	Toluene	25	36	40	90:10
3	EtOH	25	36	20	90:10
4	MeCN	25	36	78	90:10
5	DCM	25	16	95	90:10
6	DCM	20	18	95	95:05
7	DCM	10	20	94	98:02
8	DCM	0	30	50	98:02

[a] (*E*)-Ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (1.0 equiv), UHP (2.0 equiv), Quinine (0.1 equiv).
[b] Isolated yield.
[c] Diastereoselectivity ratios are based on ^{1}H NMR spectra of the crude products.

From the above observations we inferred that reacting 1.0 equiv of (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate with 2.0 equiv of UHP and 0.1 equiv of quinine at 10 °C in DCM would be the ideal condition for the reaction. The scope of the optimized condition was evaluated on various α-ylideneoxindoles bearing electron-withdrawing and donating groups which gave the benzyl/ethyl 2-oxospiro(indolin-3,2′-oxirane)-3′-carboxylate derivatives in excellent yields and high *trans* diastereoselectivity (Table 3). It was also observed that reaction did not discriminate between *N*-methyl and the bulky *N*-benzyl substituted α-ylideneoxindoles, affording good yields and diastereoselectivities in all the cases. Similar results were obtained with ethyl and benzyl ester derivatives of α-ylideneoxindoles as well.

We envisaged a plausible reaction mechanism for the formation of *trans* selective spiro-epoxyoxindoles via transition states **TS-A** and **TS-B** (Fig. 3). In **TS-A**, quinine activates the nucleophile UHP and the electrophile α-ylideneoxindole by hydrogen bonding, thereby adopting a dual activation role. The bicyclic ring nitrogen of quinine accepts hydrogen from UHP while the hydroxyl group activates the carbonyl oxygen of the amide, thus making the β-carbon of the double bond more electrophilic in nature. This is followed by the attack of the peroxide nucleophile at β-carbon, and a subsequent rotation about the sigma bond between the α and β carbons leads to the stable conformation of **TS-B**. The enolate then attacks the peroxy linkage resulting in the formation of *trans* epoxide. The hydroxide ion thus released will gain the proton from quaternary nitrogen to form a molecule of water and regenerates the quinine for next catalytic cycle.

Based on our previous work[7c] on water mediated nucleophilic reactions of epoxides, we investigated the aminolysis of the resultant *trans* epoxides. As expected the reaction led to ring opening from the less hindered β-carbon of the epoxide in aqueous

Table 1
Effect of catalysts and oxidants[a]

Entry	Catalyst (mol%)	Oxidant (equiv)	Time (h)	Yield[b] (%)	dr[c] (*trans*:*cis*)
1	A (30)	aq H_2O_2 (3.0)	36	Trace	nd
2	B (30)	aq H_2O_2 (3.0)	36	Trace	nd
3	C (30)	aq H_2O_2 (3.0)	36	Trace	nd
4	D (30)	aq H_2O_2 (3.0)	36	20	80:20
5	D (30)	aq TBHP (3.0)	36	18	85:15
6	D (30)	UHP (3.0)	12	96	90:10
7	D (30)	UHP (2.0)	12	95	90:10
8	D (20)	UHP (2.0)	14	95	90:10
9	D (10)	UHP (2.0)	16	95	90:10
10	—	UHP (2.0)	30	Trace	—

[a] (*E*)-Ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (1.0 equiv).
[b] Isolated yield.
[c] Diastereoselectivity ratios are based on ^{1}H NMR spectra of the crude products.

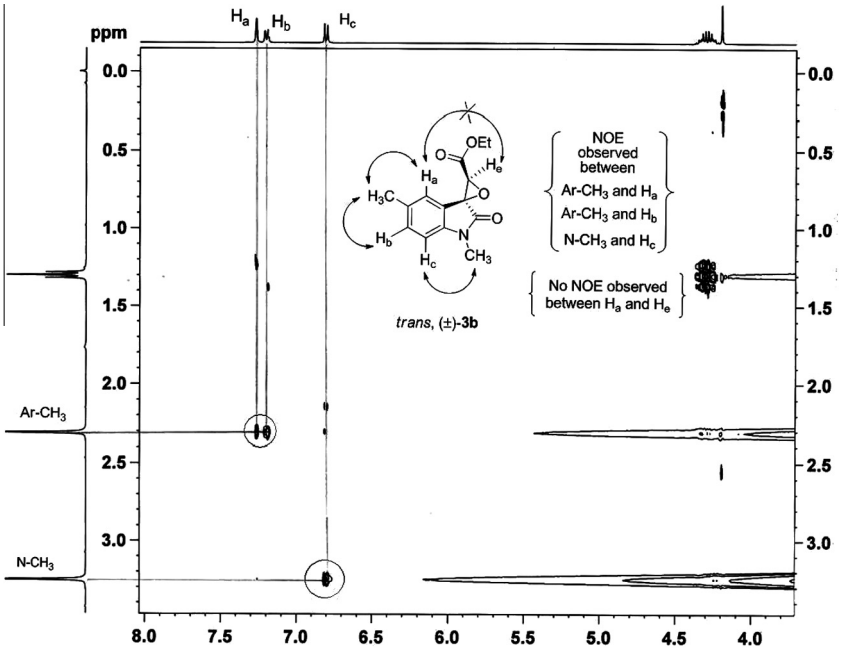


Figure 2. NOESY spectrum of the compound **3b**.

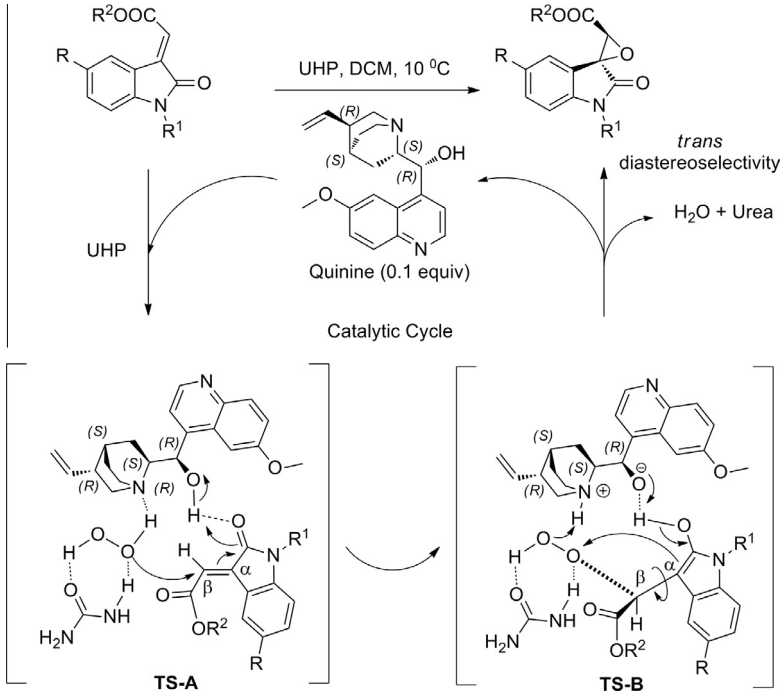
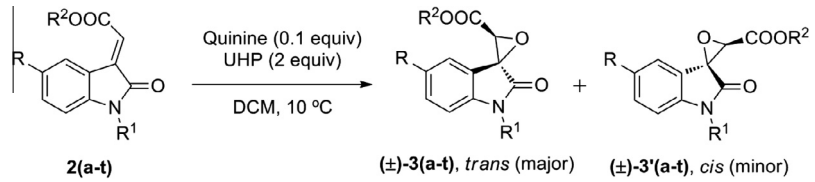


Figure 3. Plausible reaction mechanism.

medium, under sonication, to afford the product regioselectively (Table 4). The scope of the reaction was evaluated with different aniline derivatives bearing electron-withdrawing and donating groups to afford the β-hydroxy-α-amino esters with ease and high selectivity. We speculate that the hydrogen bond donor and acceptor abilities of water activate both the nucleophile and electrophile, thereby providing a dual activation role in the six membered transition state (**TS-C**), as the reactants come into close proximity.[7c,9]

In conclusion, an efficient organocatalytic dual activation approach has been developed for the diastereoselective epoxidation of (*E*)-3-ylidene-indolin-2-one derivatives using quinine (0.1 equiv) and UHP (2.0 equiv) in DCM at 10 °C to afford the spiro-epoxyoxindoles. Excellent yields and *trans* diastereoselectivity were obtained with a variety of (*E*)-3-ylidene-indolin-2-one derivatives bearing both electron-withdrawing and donating groups, without the formation of any side products. Further we have also demonstrated the regioselective aminolysis of *trans*

Table 3
Diastereoselective synthesis of benzyl/ethyl 2-oxospiro-[indolin-3,2′-oxirane]-3′-carboxylate[a]

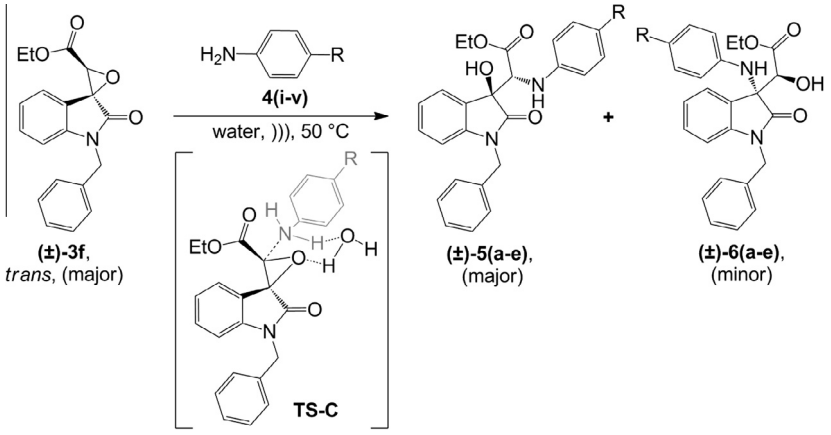


2(a-t) (±)-3(a-t), *trans* (major) (±)-3'(a-t), *cis* (minor)

Entry	R	R^1	R^2	Time (h)	Product	Yield[b] (%)	dr[c] (*trans*:*cis*)
1	H	Me	Et	16	**3a**	94	98:2
2	Me	Me	Et	24	**3b**	92	96:4
3	OMe	Me	Et	17	**3c**	90	96:4
4	Cl	Me	Et	14	**3d**	96	97:3
5	Br	Me	Et	18	**3e**	92	98:2
6	H	Bn	Et	16	**3f**	92	96:4
7	Me	Bn	Et	18	**3g**	94	96:4
8	OMe	Bn	Et	16	**3h**	92	97:3
9	Cl	Bn	Et	15	**3i**	95	98:2
10	Br	Bn	Et	18	**3j**	94	98:2
11	H	Me	Bn	22	**3k**	90	97:3
12	Me	Me	Bn	20	**3l**	95	98:2
13	OMe	Me	Bn	17	**3m**	93	96:4
14	Cl	Me	Bn	16	**3n**	96	98:2
15	Br	Me	Bn	18	**3o**	95	97:3
16	H	Bn	Bn	20	**3p**	92	97:3
17	Me	Bn	Bn	22	**3q**	93	98:2
18	OMe	Bn	Bn	18	**3r**	96	98:2
19	Cl	Bn	Bn	18	**3s**	94	96:4
20	Br	Bn	Bn	20	**3t**	90	96:4

[a] α-Ylideneoxindole (1.0 equiv), UHP (2.0 equiv), quinine (0.1 equiv), DCM (5 mL), temp 10 °C.
[b] Isolated yield.
[c] Diastereoselectivity ratios are based on ^{1}H NMR spectra of the crude products.

Table 4
Reaction of *trans* epoxide with aniline derivatives[a]



(±)-3f, *trans*, (major) (±)-5(a-e), (major) (±)-6(a-e), (minor)

Entry	Epoxide	R	Time (h)	Product	Yield[b] (%)	Ratio[c] (**5**:**6**)
1	**3f**	H	6	**5a**	86	97:03
2	**3f**	Me	8	**5b**	90	96:04
3	**3f**	OMe	8	**5c**	85	98:02
4	**3f**	Cl	5	**5d**	92	97:03
5	**3f**	Br	6	**5e**	88	98:02

[a] *trans* Epoxide (**3f**, 1.0 equiv), aniline derivatives (1.1 equiv), water (3 mL), temp 50 °C, sonication.
[b] Isolated yield.
[c] Regioselectivity ratios (**5**:**6**) are based on ^{1}H NMR spectra of the crude products.

epoxide using aniline derivatives in water, under sonication. The reaction proceeds to afford the product by opening the epoxide ring from the less hindered end. Future studies will be aimed at fine-tuning the organocatalyst to afford *trans* spiro-epoxyoxindoles with good enantioselectivity.

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Supplementary data

Supplementary data (experimental procedures, compound data and scanned spectra (^{1}H NMR, ^{13}C NMR and HRMS)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.115.

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