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Asymmetric Epoxidation of Alkylidenemalononitriles: Key Step for One-Pot Approach to Enantioenriched 3-Substituted Piperazin-2-ones

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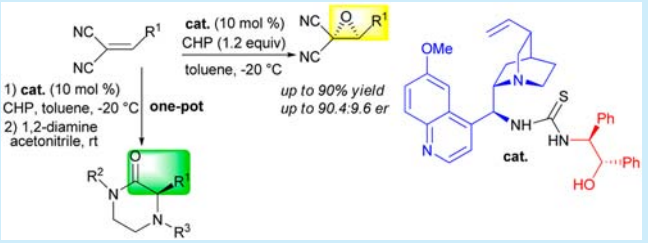
Supporting Information

ABSTRACT: The first enantioselective epoxidation of readily available alkylidenemalononitriles has been developed by using a multifunctional *cinchona* derived thiourea as the organocatalyst and cumyl hydroperoxide as the oxidant. A new simple one-pot asymmetric epoxidation/S_N2 ring-opening reaction with 1,2-diamines leading to important enantioenriched heterocycles, i.e. 3-substituted piperazin-2-ones, has been established.



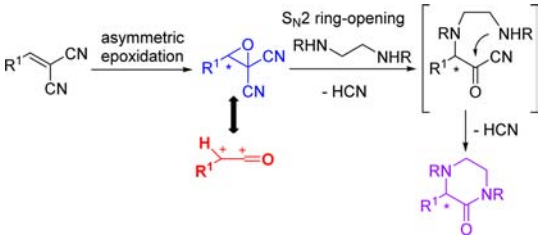
The asymmetric epoxidation of alkenes is a cornerstone transformation in organic chemistry. Several efforts have been focused in recent decades toward developing asymmetric systems for the epoxidation of a variety of substituted alkenes.[1] Different metal-based or organocatalytic protocols provide highly valuable enantioenriched epoxides as synthetic intermediates or products showing different biological activities.[1c] In terms of alkene structure, excellent stereoselective systems are currently used to epoxidize allylic and homoallylic alcohols[2] and unfunctionalized olefins.[3] In the area of asymmetric epoxidation of electron-poor alkenes, several methodologies focused on *trans*-enones.[4] Despite the success, there is room to expand the substrate scope of electron-poor alkenes, whose enantioenriched epoxides would be potentially highly attractive for further elaborations such as readily available alkylidenemalononitriles.

These alkenes are challenging Michael acceptors as demonstrated by the few methodologies reported on asymmetric carbon−carbon bond formation,[5] likely ascribed to their significant reactive nature[6] and weak H-bonding acceptor ability of the cyano group.[7] The only example by Sekiya and co-workers on an asymmetric epoxidation of alkylidenemalononitriles using alkyl hydroperoxides or molecular oxygen and stoichiometric amounts of chiral bases afforded nearly racemic epoxides in low yield.[8]

It has been demonstrated by a few reports that racemic *gem*-dicyano epoxides behave like the synthetic equivalent of dication ketenes. In the presence of binucleophilic compounds, they afforded, under reflux conditions, heterocycles such as imidazoles,[9] 2-acetylimino-1,3-oxathioles,[10] and 1,4-benzoxazin-2-ones.[11] Interestingly, Baudy-Floc'h et al. isolated a 3-aryl piperazin-2-one in 10% yield working under milder conditions.[12] The reaction proceeded at room temperature via regioselective ring-opening of the corresponding *gem*-dicyano epoxide by ethylendiamine as a binucleophile.

To address the limitations detailed above and motivated by our interest in the asymmetric synthesis of epoxides,[13] we embarked in a study aimed at the development of an enantioselective epoxidation of alkylidenemalononitriles as a primary goal. Additionally, we planned to demonstrate the feasibility of an asymmetric epoxidation of alkylidenemalononitriles as a key step for a new and straighforward access to piperazin-2-ones (Scheme 1). A regioselective S_N2 ring-opening

Scheme 1. Strategy Comprising an Enantioselective Epoxidation of Alkylidenemalononitriles Followed by a Regioselective S_N2 Ring-Opening with 1,2-Diamines



reaction of the enantioenriched *gem*-dicyano epoxides by 1,2-diamines, followed by an intramolecular attack of the other amine group to the in situ formed acyl cyanide intermediate, would lead to enantioenriched piperazin-2-ones.[14]

Developing asymmetric syntheses of substituted piperazin-2-ones is highly desirable, given their relevance as pharmacophores showing a wide range of biological activities as HDAC inhibitors,[15] bradykinin receptor antagonists,[16] serotonin receptor antagonists,[17] hepatitis C virus replication inhibitors,[18] antihelminthics,[19] and antagonist GW597599,[20] to cite a few. Additionally, they play a central role in conformationally

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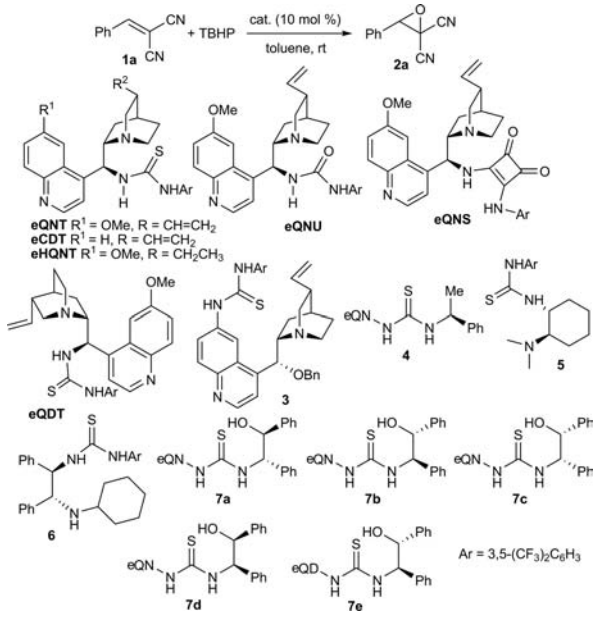
constrained peptides.[21] However, the asymmetric synthesis of substituted piperazin-2-ones is particularly challenging and only rare examples have been reported.[14f,22] Indeed, current protocols exclusively rely on classical techniques such as the use of amino acid derivatives as starting compounds, with clear limitation on structural diversity or via resolution of diastereomeric salts.[20,23]

Herein, we document our preliminary results on asymmetric nucleophilic epoxidation of alkylidenemalononitriles catalyzed by a multifunctional cinchona derived thiourea with cumyl hydroperoxide as the oxidant (CHP). The epoxides were obtained in good to high yield and up to 90:10 er. Moreover, we developed a highly valuable one-pot epoxidation/ring-opening sequence to enantioenriched 3-substituted piperazin-2-ones starting from easily accessible alkylidenemalononitriles.

We reasoned that bifunctional catalysts bearing double H-bonding donors would have been effective in engaging a H-bonding network with alkylidenemalononitrile. This idea was supported by our recently disclosed ability of cinchona derived thioureas to catalyze the enantioselective nucleophilic epoxidation of electron-poor 1,1-disubstituted terminal alkenes with *tert*-butyl hydroperoxide (TBHP).[13d] Initial experiments were performed with phenylidenemalononitrile **1a** and TBHP in toluene at room temperature screening different organocatalysts at a 10 mol % loading (Table 1). We were pleased to observe that *epi*-quinine derived thiourea **eQNT** satisfactorily catalyzed the reaction affording the epoxide with a 67.5:32.5 er value (entry 1). The corresponding urea and squaramide proved to be slightly less efficient (entries 2 and 3). The *epi*-cinconidine thiourea **eCDT** and *epi*-hydroquinine thiourea **eHQNT** were less effective (entries 4 and 5), whereas the pseudoenantiomeric *epi*-quinidine thiourea **eQDT** afforded the opposite enantiomer of the epoxide in high yield but with lower enantioselectivity (entry 6). Catalyst **3**, where the thiourea moiety is positioned in the quinoline ring, proved to be the worst in the series, indicating that the quinuclidine nitrogen and hydrogen bonding donating groups are catalytically more effective when located in proximity (entry 7). The presence of a chiral amine moiety in the *epi*-quinine derived thiourea **4** was detrimental for the enatioselectivity (entry 8). These results suggested that additional chiral scaffolds could be exploited for matching effects on the catalyst activity. Structurally different thiourea amines **5** and **6** (entries 9 and 10) did not improve the result obtained with **eQNT** (entry 1). Taking into account the reactive nature of alkylidene malononitrile, we thought improvements might be achieved using amine thioureas bearing multiple hydrogen-bonding donors incorporating chiral aminoalcohol moieties.[24] We investigated the catalytic activity of *epi*-quinine derived thioureas **7a**–**e** under the standard conditions (entries 11–15). Interestingly, promoter **7a** proved to be more active and enantioselective than **eQNT** (entry 11), with the best matching effect displayed by the (*S*,*S*)-amino alcohol portion. The absolute configuration of the amino alcohol moiety plays an important role as the opposite enantiomer of **2a** was obtained when passing from catalyst **7a** to **7b**, containing the enantiomeric amino alcohol moiety (entries 11 and 12). The pseudoenantiomeric catalyst **7e** (with respect to **7a**) nicely led to the formation of the opposite enantiomer of product **2a** with the same level of enantioselectivity (entry 15).

Extensive screening of the reaction parameters,[25] choosing catalyst **7a** as the best performing promoter, enabled identification of cumyl hydroperoxide (CHP) as the best

Table 1. Screening of Catalysts in the Asymmetric Epoxidation of Alkene 1a[a]



entry	cat.	time/h	yield/%[b]	er/%[c]
1	**eQNT**	15	58	67.5:32.5
2	**eQNU**	16	48	65.4:34.6
3[d]	**eQNS**	40	70	62.2:37.8
4	**eCDT**	21	57	59.5:40.5
5	**eHQNT**	24	63	56.2:43.8
6[e]	**eQDT**	21	84	44.9:55.1
7	**3**	29	43	54.2:45.8
8	**4**	15	72	52.4:47.6
9[e]	**5**	24	55	44.3:55.7
10[e]	**6**	24	34	31.3:68.7
11	**7a**	21	90	77.2:22.8
12[e]	**7b**	22	80	42.8:57.2
13	**7c**	18	75	71:29
14[e]	**7d**	17	74	49.8:50.2
15[e]	**7e**	16	87	23:77

[a]Reactions were carried out at 0.1 mmol scale of **1a** (*C* 0.2 M) using TBHP (1.2 equiv). [b]Determined by ^{1}H NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as an internal standard. [c]Determined by chiral HPLC analysis. [d]Reaction carried out with 5 mol % of **eQNS** in $CHCl_3$. [e]The opposite enantiomer was preferentially obtained.

oxidant, working in toluene at −20 °C. Under optimized conditions, we studied the substrate scope of the asymmetric epoxidation of alkylidenemalononitriles (Table 2). Differently phenyl substituted alkenes were generally converted into the corresponding epoxides in good to high yield and moderate to good enantiomeric ratio irrespective of the substitution pattern. The *ortho*-substituted derivative was obtained with only a slightly decreased enantiomeric ratio (entry 9). In the case of the 4-cyano substituted derivative, the epoxide was isolated with up to 90:10 er (entry 6). Access to both enantiomeric products is an important added value of an asymmetric methodology, especially in view of the potential biological activity of the final compounds or their derivatives. Pseudoenantiomeric cinchona alkaloid catalysts seldom afford the opposite enantiomer of a product with the same level of enantioselectivity. When the pseudoenantiomeric catalyst **7e** was used, we were pleased to recover the opposite enantiomer

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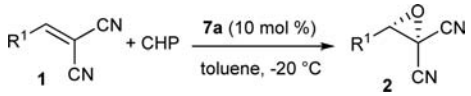
Table 2. Asymmetric Epoxidation of Alkylidenemalononitriles with 7a/CHP System[a]



entry	R^1	time/h	yield **2**/%[b]	er **2**/%[c]
1	Ph	24	78 (**a**)	85.2:14.8
2	4-$CF_3C_6H_4$	28	74 (**b**)	86:14
3	3-BrC_6H_4	21	90 (**c**)	83:17
4	2-naphthyl	42	70 (**d**)	81.6:18.4
5	4-$NO_2C_6H_4$	26	64 (**e**)	85.5:14.5
6[d]	4-CNC_6H_4	20	80 (**f**)	90.4:9.6
7[d,e]	4-CNC_6H_4	25	79 (**f**)	90.1:9.9
8	4-ClC_6H_4	22	80 (**g**)	87.7:12.3
9	2-MeC_6H_4	43	65 (**h**)	82.8:17.2
10	3-$MeOC_6H_4$	64	90 (**i**)	86.6:13.4
11	cyclohexyl	67	84 (**j**)	82:18
12	*n*-C_7H_{15}	45	47 (**k**)	74.9:25.1

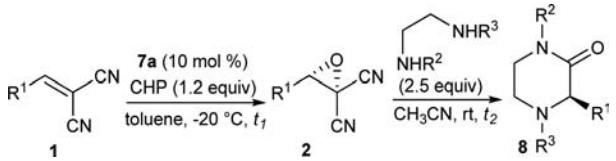
[a]Reactions were carried out at 0.15 mmol scale of **1** (*C* 0.05 M) using CHP (1.2 equiv). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]A mixture of toluene/CH_2Cl_2 3/1. [e]The opposite enantiomer was preferentially obtained.

of epoxide **2f** with the same e.r. value (entry 7). Surprisingly, less reactive and more challenging aliphatic alkylidenemalononitriles were suitable substrates for the epoxidation, which proceeded with a slight decrease in the enantiocontrol (entries 11 and 12).

We next investigated the synthetic potential of this class of epoxides to rapidly and conveniently access the piperazin-2-one scaffold in an one-pot access,[26] as illustrated in Scheme 1. After performing the asymmetric epoxidation of representative alkylidenemalononitriles under standard conditions, toluene was removed under reduced pressure and replaced with acetonitrile followed by the addition of 2.5 equiv[27] of 1,2-diamines at room temperature (Table 3).

We were delighted to isolate in good overall yield the corresponding *N*-benzyl substituted heterocycles **8** using *N*-dibenzyl-1,2-ethylendiamine and different arylidenemalononitriles **1** (entries 1−3). More importantly, the ring-opening reaction occurred stereospecifically, according to an S_N2 displacement, as attested by the enantiomeric ratio values observed for compounds **8**. *N*-Unsubstituted piperazin-2-one **8d** was also isolated in high overall yield without erosion of enantioselectivity using ethylendiamine as the binucleophile (entry 4). Interestingly, when reacting unsymmetric *N*-benzyl ethylendiamine with model epoxide **2a**, the regioisomer (R^2 = Bn, R^3 = H) derived from epoxide ring-opening by the less sterically demanding nitrogen of the diamine was almost exclusively obtained (entry 5). On the basis of characterization data of previously reported compounds **8a**,**d**[22a,b] the absolute configuration of the stereocenter was established to be (*R*) and consequently the absolute configuration of epoxide as (*S*)-**2a**. Finally, (1*R*,2*R*)-1,2-diaminocyclohexane reacted with epoxide **2a** affording two enantiomerically pure bicyclic diastereoisomers **8f** and **8g** in 84% and 14% yield respectively, in line with the enantiomeric ratio of epoxide **2a**. In addition, we confirmed the (*S*)-absolute configuration of epoxide **2a**, comparing the data of diastereoisomers **8f**,**g** with data previously reported for enantiomerically pure diastereoisomer **8g**.[14c]

Table 3. One-Pot Asymmetric Epoxidation/Ring-Opening Reaction to 3-Substituted Piperazin-2-ones[a]



entry	R^1	R^2, R^3	t_1,t_2/h	yield **8**/%[b]	er **8**/%[c]
1	Ph	Bn, Bn	30, 21	60 (**a**)	85.9:14.1
2	4-CNC_6H_4	Bn, Bn	29, 19	67 (**b**)	88.9:11.1
3	4-ClC_6H_4	Bn, Bn	29, 20	70 (**c**)	87.8:12.2
4	Ph	H, H	30, 45	85 (**d**)	85.9:14.1
5[d]	Ph	Bn, H	30, 32	76 (**e**)	85.1:14.9
6[e]	Ph		36, 22	84 (**f**) 14 (**g**)	

[a]Reactions were carried out at 0.15 mmol scale of **1** (*C* 0.05 M) using CHP (1.2 equiv) at −20 °C for the indicated time (t_1). After removing toluene, CH_3CN (5 mL) and 1,2-diamine (2.5 equiv) were added, while stirring was maintained at room temperature for the indicated time (t_2). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The regioisomeric ratio of 92:8 was determined by ^1H NMR analysis. [e](1*R*,2*R*)-1,2-Diaminocyclohexane (2 equiv) was used.

On the basis of experimental data, a plausible transition state model for the oxa-Michael step of the nucleophilic epoxidation is illustrated in Figure 1. The alkylidenemalononitrile is

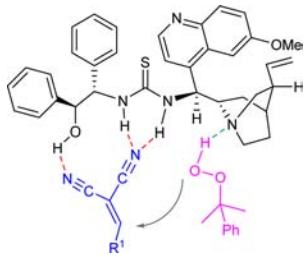


Figure 1. Postulated transition state model.

activated and oriented by a H-bonding network of the thiourea NH and the OH bonds.[28] The OH group of the CHP is expected to be strongly engaged in H-bonding interaction with the basic quinuclidine nitrogen. The attack of the peroxide would preferentially occur to the *Si*-face of the alkene, to give the enolate which after ring closure would provide the (*S*)-epoxide.

In conclusion, we disclosed the first asymmetric epoxidation of readily available alkylidenemalononitriles catalyzed by a multifunctional cinchona alkaloid thiourea/CHP system. The epoxidation is applicable to either aromatic and aliphatic alkylidenemalononitriles achieving the products in both absolute configurations with a moderate to good level of enantiocontrol. A relevant synthetic application of these products has been also documented. Either *N*-alkylated or *N*-unprotected enantioenriched 3-substituted piperazin-2-ones can be satisfactorily isolated starting from alkylidenemalononitriles, via a one-pot epoxidation/S_N2 ring-opening reaction sequence. Our approach to 3-substituted piperazin-2-ones can be considered complementary to the asymmetric reduction of

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the aliphatic trichloromethyl ketones/Jocic type reaction sequence.[14f,29] Further work to improve the enantioselectivity and extend the scope of the synthetic elaborations is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02186.

Experimental details, analytical data, copies of ^{1}H, ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(25) See Tables S1−S4 in the Supporting Information.

(26) For notable examples of organocatalytic pot-economic synthesis of biologically active products, see: (a) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304−1307. (b) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450−3452. (c) Weng, J.; Wang, S.; Huang, L.-J.; Luo, Z.-Y.; Lu, G. *Chem. Commun.* **2015**, *51*, 10170−10173.

(27) A slight excess of the diamine was used to remove HCN formed in the course of the reaction.

(28) Hydrogen bonding between each cyano group with a single NH of the thiourea moiety was reported to be less plausible by a recent DFT study; see: Qi, Z.-H.; Zhang, Y.; Ruan, G.-Y.; Zhang, Y.; Wang, Y.; Wang, X.-W. *RSC Adv.* **2015**, *5*, 34314−34318.

(29) Jocic, Z. *Zh. Russ. Fiz. Khim. Ova.* **1897**, *29*, 97−103.

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