Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201601083
Internationale Ausgabe: DOI: 10.1002/anie.201601083

Dysprosium(III)-Catalyzed Ring-Opening of *meso*-Epoxides: Desymmetrization by Remote Stereocontrol in a Thiolysis/Elimination Sequence

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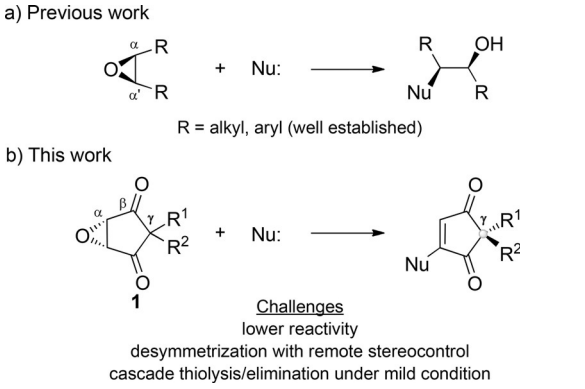
Abstract: *An unprecedented asymmetric desymmetrization of meso-epoxides, derived from cyclopentene-1,3-diones, with 2-mercaptobenzothiazoles has been realized. It was efficiently catalyzed by a chiral Dy^{III}/N,N′-dioxide complex through a thiolysis/elimination sequence. This remote stereocontrol strategy provides facile access to synthetically versatile cyclopentene derivatives bearing an all-carbon quaternary stereogenic center in high yield and excellent enantioselectivity. Intriguingly, optically active thiophene could be readily generated from the obtained product through an efficient one-pot protocol.*

The nucleophilic ring-opening of epoxides[1] represents an important strategy in organic synthesis because of its powerful capability in forming bonds. This process leads to the possible formation of two adjacent stereocenters at the α,α′-positions of the *meso*-epoxide (Scheme 1 a). As such, considerable efforts have been devoted to the enantioselective desymmetrization of *meso*-epoxides over the past few decades by using highly efficient catalytic systems and include a variety of nucleophiles. The usual substituent group of the *meso*-epoxide is either alkyl or aryl, for example, *cis*-cycloalkane or *cis*-stilbene. However, these approaches are limited when R = carbonyl group.[2] The lack of related literature is most likely because of the lower reactivity of the oxirane ring on diketoepoxides compared with that of normal epoxides, and therefore the ring-opening process of diketoepoxides requires harsh reaction conditions.[3] To the best of our knowledge, such catalytic enantioselective reactions remain elusive to date. Therefore, the asymmetric ring-opening of *meso*-diketoepoxides is challenging and in high demand.



Scheme 1. Asymmetric desymmetrization of prochiral *meso*-epoxides by nucleophilic ring-opening (previous work) and a thiolysis/elimination sequence (this work).

As the 2,2-disubstituted cyclopentene-1,3-dione bearing an all-carbon quaternary stereogenic center is ubiquitous in many biologically active compounds and pharmaceuticals,[4] a direct method towards these chiral motifs would be important. Among various strategies which have been used for accessing such moieties, asymmetric desymmetrization[5] is undoubtedly an ideal strategy because of its step economy and the efficiency in construction of the all-carbon stereogenic centers. There have been only two reports so far. Mukherjee[6] and co-workers reported an elegant study in alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-dione in the presence of a bifunctional tertiary aminourea catalyst. Soon after, Lee and co-workers[7] reported the desymmetrization of such a motif through an oxidative heck coupling process, albeit with moderate enantioselectivity. Therefore, the development of a new desymmetrization method capable of accessing chiral 2,2-disubstituted cyclopentene-1,3-diones is still of great significance. Given our interest in the construction of all-carbon quaternary centers,[8,9] we speculated that the asymmetric nucleophilic ring-opening of the readily available *meso*-epoxides **1** followed by subsequent dehydration would directly afford the cyclopentene-1,3-dione bearing an all-carbon quaternary stereogenic center (Scheme 1 b). However, several challenges had to be overcome in this design: 1) lower reactivity of *meso*-diketoepoxides towards nucleophilic attack; 2) stereoselective construction of an all-carbon quaternary stereogenic center (γ-position) which is remote from the reaction site; 3) the thiolysis/dehydration sequence must proceed under mild reaction conditions with a broad substrate scope. Herein, we report an unprecedented desymmetrization by remote stereocontrol for synthesizing a variety of cyclopentene-1,3-diones, and it is capable of generating an all-carbon quaternary stereogenic center through an efficient thiolysis/elimination sequence.

As no example of a catalytic desymmetrization of *meso*-diketoepoxides has been reported so far, a sufficient screening of reaction conditions was carried out to estimate the

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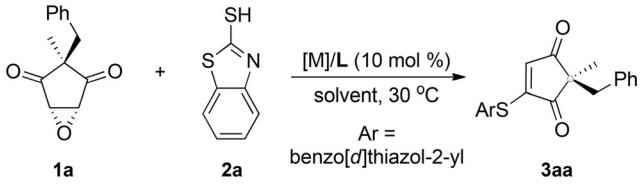
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201601083.

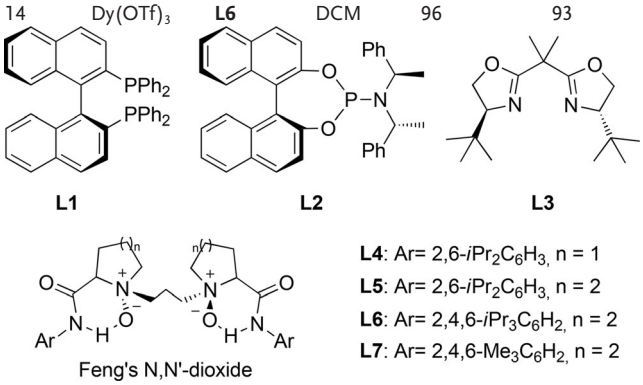
feasibility of this proposal. The diketoepoxide *anti*-**1a**, which could be easily generated from cyclopentene-1,3-dione in good yields with high *anti* configuration, was employed. Initial investigations were focused on the nucleophiles and chiral phosphoric acids (CPA) as the catalysts. With different types of nucleophiles screened, most of them ($TMSN_3$, aniline, phenol, indole, and etc.) failed to open the oxirane ring, probably because of the lower reactivity of either the epoxide or the nucleophile. Inspired by the elegant work reported by Sun and co-workers,[10] 2-mercaptobenzothiazole (**2a**) was selected as the nucleophile in the model reaction. We were pleased to find that the ring opening was followed by a spontaneous elimination process, thus affording a high yield of the cyclopentene-1,3-dione **3aa**, which featured an all-carbon quaternary stereogenic center. And the benzothiazole thioether moiety in the corresponding product is frequently found in antimycobacterial compounds.[11] Unfortunately, only moderate enantioselectivity was achieved (see the Supporting Information for more details) with the tested chiral phosphoric acids. Then, we turned our attention into transition-metal catalysts. Several classical privileged chiral ligands were employed using $Sc(OTf)_3$ as the metal salt. However, the product **3aa** was obtained either in racemic form or in poor enantioselectivity with the P,P-ligand (**L1**), N,P-ligand (**L2**), and N,N-ligand (**L3**) (Table 1, entries 1–3). Considering Feng's N,N′-dioxide chiral ligands,[12] which exhibit excellent asymmetric induction in numerous transition metal catalyzed asymmetric reactions, the N,N′-dioxide **L4** was tested. To our delight, the reaction proceeded successfully to deliver the desired product in high yield with 72% *ee* (entry 4). Encouraged by this promising result, a series of N,N′-dioxides were investigated. It was found that increasing the steric hindrance of the subunits on amide could significantly improve the enantiocontrol (entries 5–7). Dichloromethane turned out to be the ideal solvent in this reaction (entries 8 and 9). Then, the lanthanide triflates were investigated to further improve the enantioselectivity (entries 10–14). When the metal salt was changed to $Dy(OTf)_3$, the desired product was isolated in 96% yield and 93% *ee* (entry 14). Therefore, the optimal reaction conditions for this thiolysis/elimination reaction requires $Dy(OTf)_3$/**L6** (10 mol %) as the catalyst in dichloromethane at 30°C for 2 hours.

After the optimal reaction conditions were established, we started to evaluate the reaction scope. As revealed in Table 2, ring-opening/dehydration of a series of *meso*-epoxides (**1**) derived from cyclopentene-1,3-diones with 2-mercaptobenzothiazole (**2a**) was investigated. The benzyl group bearing electron-rich (entries 7–9, and 12), electron-neutral (entry 1), and electron-deficient (entries 3–6) substituents in **1** were all well-tolerated. Notably, the substitution pattern almost had no effect on the yield or stereoselectivity, thus the corresponding products could be obtained in excellent yield (92–99%) with excellent enantioselectivity (90–94% *ee*). In addition, naphthyl-substituted epoxides were also suitable in this reaction, thus giving the desired product in excellent yield and enantioselectivity (93–97% yield, 92–92% *ee*, entries 10 and 11). Remarkably, the substrate scope was not limited to the benzylic substitutents, and result shows that 92% yield

Table 1: Optimization of the reaction conditions.[a]



Entry	M	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	$Sc(OTf)_3$	**L1**	DCM	87	3
2	$Sc(OTf)_3$	**L2**	DCM	89	13
3	$Sc(OTf)_3$	**L3**	DCM	86	0
4	$Sc(OTf)_3$	**L4**	DCM	96	72
5	$Sc(OTf)_3$	**L5**	DCM	95	78
6	$Sc(OTf)_3$	**L6**	DCM	96	82
7	$Sc(OTf)_3$	**L7**	DCM	94	57
8	$Sc(OTf)_3$	**L6**	PhMe	81	54
9	$Sc(OTf)_3$	**L6**	Et_2O	94	28
10	$La(OTf)_3$	**L6**	DCM	96	72
11	$Y(OTf)_3$	**L6**	DCM	92	82
12	$Ni(OTf)_2$	**L6**	DCM	87	10
13	$Gd(OTf)_3$	**L6**	DCM	95	92
14	$Dy(OTf)_3$	**L6**	DCM	96	93



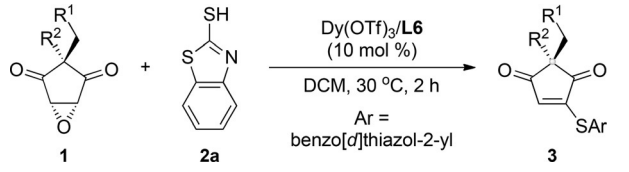
[a] All reactions were carried out with 0.10 mmol of **1a** and 0.11 mmol of **2a** in 1 mL solvent for 2 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis.

with 90% *ee* were observed in the product when an epoxide containing an allyl group at the stereocenter was used in this reaction (entry 13). The propyl-substituted epoxide **1n** was also compatible, thus affording **3an** in 99% yield with 94% *ee* (entry 14). Notably, perfect desymmetrization could be efficiently realized even when there is subtle difference between the two substituted groups in **1o** (entry 15). Moreover, the methyl group at the stereocenter could be replaced by an ethyl group, thus providing the cyclopentene-1,3-dione **3ab** in 96% yield with 93% *ee* (entry 2).

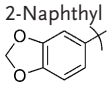
Various aryl 2-mercaptobenzothiazoles[13] (**2**) were also investigated (Table 3). Different of substitutents at the 5-, 6-, and 7-positions on the benzothiazole framework were all well-tolerated. Reaction of aryl mercaptans containing methyl (**2h**, **2f**), methoxy (**2b**), ethoxy (**2d**), chloro (**2c**, **2g**), and even methyl,bromo disubstitution (**2e**) all gave the the corresponding products **3** in excellent yields and enantioselectivities. Single-crystal X-ray analysis of compound **3aa**[14] allowed us to establish the all-carbon quaternary stereogenic center as having an *R* configuration (Figure 1).

All the epoxides used thus far have had an *anti* arrangement on the ring, and to gain insight into the stereochemistry

Table 2: Substrate scope of asymmetric desymmrtrization.[a]



1 2a 3

Entry	1		3	Yield [%][b]	*ee* [%][c]
	R^1	R^2			
1	Ph	Me (**1a**)	**3aa**	96	93
2	Ph	Et (**1b**)	**3ab**	97	92
3	*o*-BrC_6H_4	Me (**1c**)	**3ac**	95	93
4	*m*-BrC_6H_4	Me (**1d**)	**3ad**	94	92
5	*p*-$CF_3C_6H_4$	Me (**1e**)	**3ae**	92	90
6	*m*-ClC_6H_4	Me (**1f**)	**3af**	95	92
7	*o*-$CH_3C_6H_4$	Me (**1g**)	**3ag**	99	92
8	*m*-$CH_3C_6H_4$	Me (**1h**)	**3ah**	99	94
9	*p*-CH_3-C_6H_4	Me (**1i**)	**3ai**	98	92
10	1-Naphthyl	Me (**1j**)	**3aj**	93	92
11	2-Naphthyl	Me (**1k**)	**3ak**	97	92
12		Me (**1l**)	**3al**	98	92
13	CH_2=CH	Me (**1m**)	**3am**	92	90
14	Et	Me (**1n**)	**3an**	99	94
15	Me	Me (**1o**)	**3ao**	97	90

[a] All reactions were carried out with 0.10 mmol of **1** and 0.11 mmol of **2a** in 1 mL DCM. [b] Yield of isolated prodcut. [c] Determined by HPLC analysis.

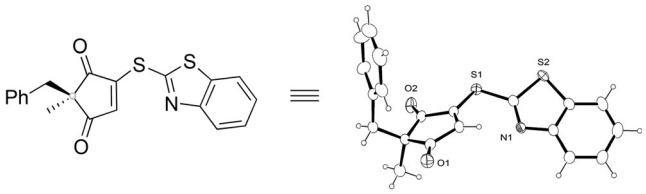
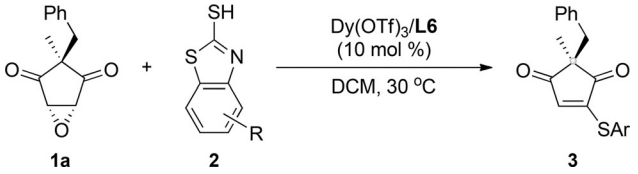


Figure 1. The absolute configuration of (*R*)-**3aa**.[14]

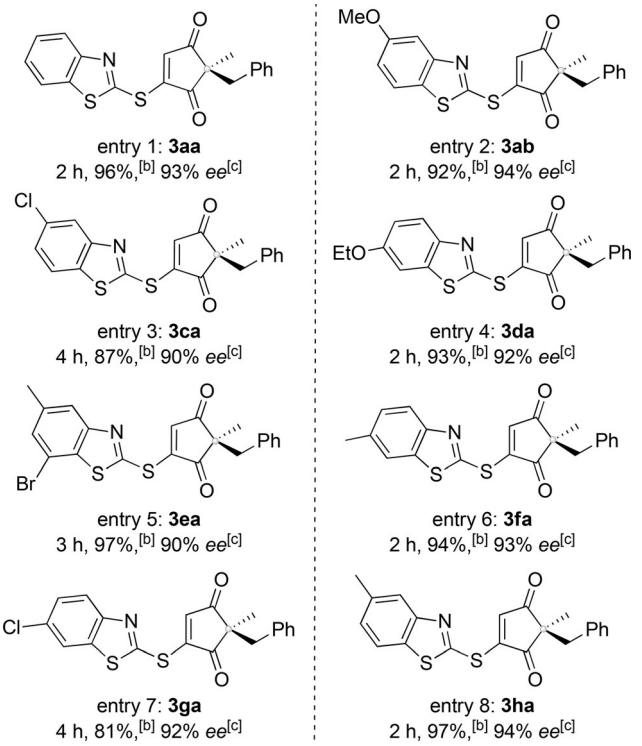
of this cascade thiolysis/elimination process, we studies of the behavior of the corresponding *syn* epoxides. We believe that increasing the steric bulk of the substitutents on the quaternary carbon center in the cyclopentene-1,3-dione would allow the formation of the *syn* epoxide. As expected, the epoxide **1b**, containing an ethyl group, and **1c**, containing an *ortho*-bromo-substituted phenyl group, were observed in 1:1 ratio of *anti*/*syn*, and the geometry of *anti*-**1c** and *syn*-**1c** were validated by X-ray structure analysis[14] (see the Supporting Information for details). Interestingly, changing the geometry of either the epoxide **1b** or **1c** from *anti* to *syn* under the standard reaction conditions led to the formation of the enantiomer (*S*)-**3**, albeit with moderate enantioselectivity (Scheme 2).

To further demonstrate the potential utility of this methodology, the reaction between (*anti*)-**1a** and **2a** were carried out on a gram scale, and (*R*)-**3aa** was isolated in high yield with similar enantioselectivity (Scheme 3). Treatment of (*R*)-**3aa** with mercaptoacetaldehyde and a catalytic amount of DABCO, followed by the addition of 1 equivalent of TsOH led to the formation of the optically active thiophene **4**, which

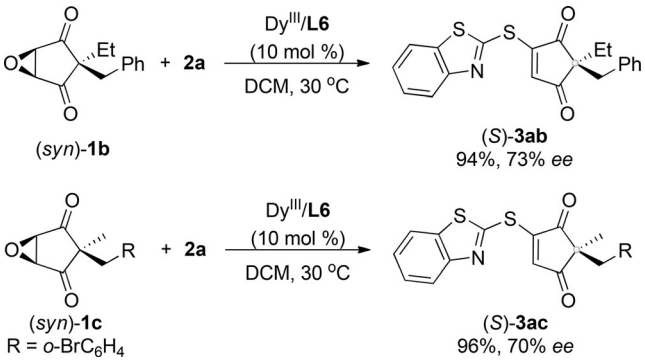
Table 3: Scope with respect to thr substrates.[a]



1a 2 3

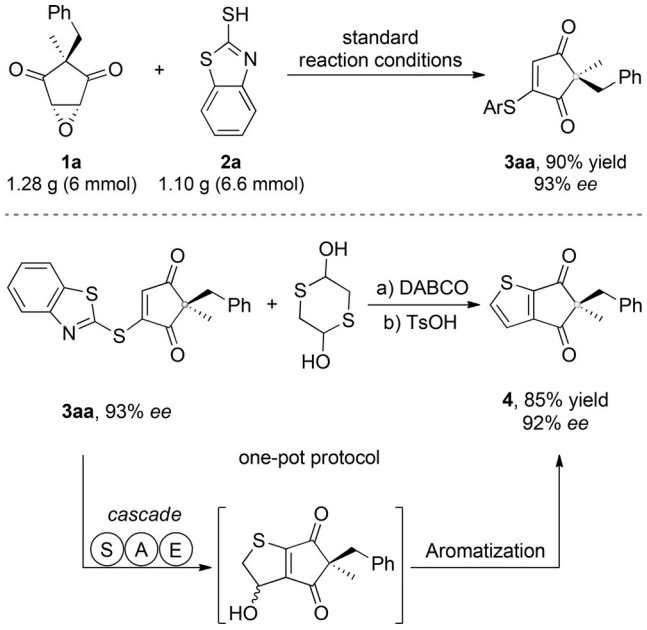


[a] All reactions were carried out with 0.10 mmol of **1a** and 0.11 mmol of **2** in 1 mL solvent. [b] Yield of isolated product. [c] Determined by HPLC analysis.



Scheme 2. The stereochemistry with epoxide (*syn*)-**1b** and (*syn*)-**1c**.

is commonly found in materials science and pharmaceuticals.[15] The formation of the thiophene resulted from a base-promoted sulfa-Michael addition/aldol/elimination (SAE) sequence followed by subsequent acid-promoted aromatization, in which benzothiazole thioether moiety served as a good leaving group. Notably, this reaction could be performed in one pot, thus affording **4** in 85% yield without loss in the enantiomeric excess.



Scheme 3. Scale-up and one-pot synthesis of optically active thiophene **4**.

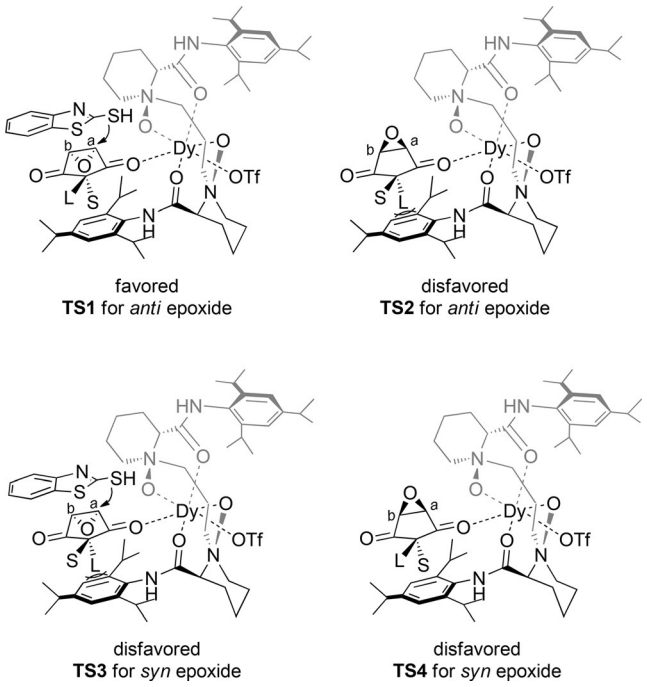


Figure 2. Proposed transition state.

Based on the above control experiments, X-ray structures of (*R*)-**3aa**, (*anti*)-**1c**,vand (*syn*)-**1c**, and literature results,[12] a possible transition state is proposed (Figure 2): the coordination of the tetradentate chiral ligand **L6** and (*anti*)-**1** to the dysprosium(III) center gives rise to an active octahedral complex. The coordination of **1** leads to lower electron density at carbon atom a than at b, and allows the nucleophile to attack the epoxide at **a** from the backside to afford **3aa** with an *R* configuration (**TS1**). On the contrary, the transition-state **TS2** is disfavored because of the steric congestion between the benzyl group of the epoxide and aryl group of the ligand. Meanwhile, the backside of (*anti*)-**1** is shielded by the neighboring amide group of the ligand and thus makes the nucleophilic attack disfavored. For the *syn* epoxide, the 2,4,6-triisopropylaniline of the ligand either shield the backside of the epoxide or cause the steric congestion with the substituted group of the epoxide, thus both the transition-state **TS3** and **TS4** are unfavorable and explains the lower enantioselectivity with the corresponding *syn* epoxide.

In summary, we have developed an unprecedented asymmetric thiolysis/elimination sequence for *meso*-diketoepoxides derived from cyclopentene-1,3-diones. This desymmetrization by remote stereocontrol was efficiently promoted by a chiral N,N′-dioxide/dysprosium(III) complex. Because of the broad substrate scope, step economy, and mild reaction conditions, this cascade reaction occupies an important position in the construction of enantioenriched natural and biologically active compounds containing cyclopentene-1,3-dione units. Furthermore, the achieved product can be easily transformed into optically active thiophene in a one-pot protocol without losing of enantiomeric excess. Further studies of this ring-opening process with other nucleophiles and application in organic synthesis are ongoing in our laboratory.

Acknowledgements

This work was supported by NSFC (21372180, 21525207), and the Fundamental Research Funds for the Central Universities. The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated. We thank Prof. Xiao-Ming Feng, Prof. Xiao-Hua Liu at Sichuan University for providing the N,N′-dioxide **L6** and Prof. Hua Li at Wuhan University for solving the crystal structures.

Keywords: asymmetric catalysis · dysprosium · enantioselectivity · heterocycles · N ligands

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5829–5833
Angew. Chem. **2016**, *128*, 5923–5927

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Received: January 30, 2016
Published online: April 6, 2016

