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Highly stereoselective *syn*-ring opening of enantiopure epoxides with nitric oxide

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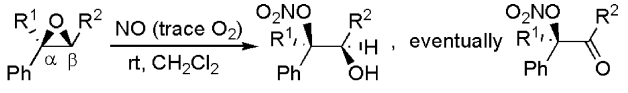
Abstract—Reaction of enantiopure epoxides (**1**) with NO occurred highly stereoselectively, affording *syn*-ring opened products, nitrates (**2**). The configuration of **2** was confirmed to be retained by determining the configuration of reduced products 1,2-glycols (**4**) from **2**. A possible mechanism is suggested to trace out the *syn*-ring opening pathway.

Nitric oxide (NO) has been explored to be capable of reacting with various organic compounds such as olefines,[1] amines,[2] amides,[3] oximes,[4] enamines,[5] arylhydrazines,[6] and arylhydrazones.[7] Our recent studies have given some insight into the distinct ring opening setereoselectivities of epoxides and aziridines upon reaction with NO.[8,9] NO led to the *syn*-selective ring opening of 2,3-epoxy phenyl ketones, giving *syn*-α-hydroxy nitrates,[8] whereas epoxides bearing a secondary carbon atom at C-2[10] and aziridines[9] underwent *anti*-selective ring opening to afford *anti*-α-hydroxy and *anti*-α-*N*-tosyl nitrates, respectively. These results clearly indicate that the *syn* or *anti*-selective ring opening fashion of epoxides is strongly dependent on C2-substituent. It was still found that epoxides were converted into β-hydroxy nitrates with cerium ammonium nitrate (CAN) in good yields in an *anti*-ring opening manner.[11,12] Hence, to obtain a clear insight into the ring opening reaction of epoxides with NO is of significance. We have further investigated the reaction of NO with various enantiopure epoxides (**1**).[13,14] The resulting nitrates with retention of configuration are obtained. To our best knowledge, there has still no report pertinent to the reactions of NO with asymmetric organic molecules.

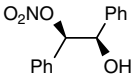
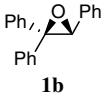
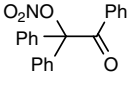
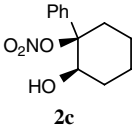
Furthermore, organic nitrates belong to the oldest class of NO donors applied to clinical purposes and have long been used to relive angina pectoris. All the major biological effects of organic nitrates have been referred to the formation of NO. Otherwise, nitrates have been widely applied to organic syntheses[15] and used as effective protecting groups for hydroxy groups.[11] In general, organic nitrates have been readily prepared from the esterification of corresponding alcohols or substitution of reactive alkyl halides by $AgNO_3$.[16] Yet, β-hydroxy nitrates were obtained in unsatisfactory yields by the reaction of nitrating agents with epoxides.[17]

The results are collected in Table 1. It is particularly noteworthy that the reaction proceeded with the

Table 1. Ring opening of enantiopure epoxides by NO



1 2 3

Entry	Epoxide	Nitrate ester	Time (day)	Yield[a] (%)
1	 **1a**	 **2a**	5	79.8[b]
2	 **1b**	 **3b**	5	72.3[c]
3	 **1c**	 **2c**	5	60.2[d]

(*continued on next page*)

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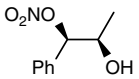
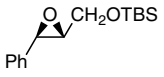
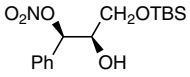
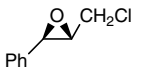
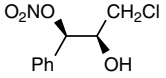
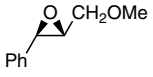
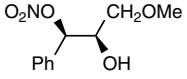
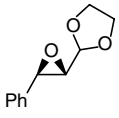
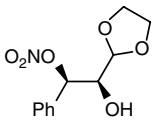
Table 1 (*continued*)

Entry	Epoxide	Nitrate ester	Time (day)	Yield[a] (%)
4	 **1d**	 **2d**	3	74.0
5	 **1e**	 **2e**	5	87.8
6	 **1f**	 **2f**	5	36.6
7	 **1g**	 **2g**	5	84.1
8	 **1h**	 **2h**	3	80.8

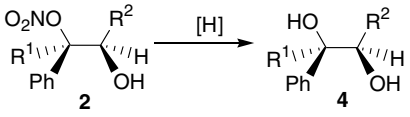
[a] Isolated yield after silica gel chromatography.
[b] Along with 20.0% of 2,2-diphenylacetaldehyde.
[c] Along with 7.2% of 2-hydroxy-1,2,2-triphenylethanone.
[d] Along with 12.0% of (1*R*,2*R*)-1-phenylcyclohexane-1,2-diol.

retention of configuration at the benzyl position. By comparison, configuration inversions were observed in other epoxide opening reactions.[10–12,18] Except for **1b**, the reaction exclusively afforded *erythro*-β-hydroxy nitrates (**2**) in moderate yields (Table 1). Table 1 demonstrates that reactions provided poor yields when the β-site beared an electron-withdrawing group, such as **1f**. In particular, diaryl or triaryl substituted epoxides gave a few by-products. For instance, in the case of **1a**, the reaction afforded 2,2-diphenylacetaldehyde. Otherwise, **1b** was converted into **3b**, a ketone. In the case of **1c**, a small amount of **4c**, an 1,2-glycol, was obtained.

We started with an enantiopure **1** (Table 1). There were several possible outcomes: retention or inversion of stereochemistry. In order for the absolute configuration of **2** to be specified, **2** was reduced to the corresponding 1,2-glycols (**4**)[11,19] with high ee and dr values (Table 2) using various reductants such as NH_2NH_2, $NaBH_4$, $LiAlH_4$, or $(NH_4)_2S$.[20] The optical rotation of **4** was measured and their stereochemistry was determined to be retained by comparing the measured values with those reported. It is only possible to infer that epoxides were opened in *syn* fashion by NO. Ammonium sulfide showed to be more favorable for the reduction of nitrates to glycols. It gave the reducing products in quantitative yields and with high ee values (Table 2, entry 4). It is noticed that **3b** was not reduced by the above reductants and **2c** was unstable and directly converted into **4c** by standing overnight.

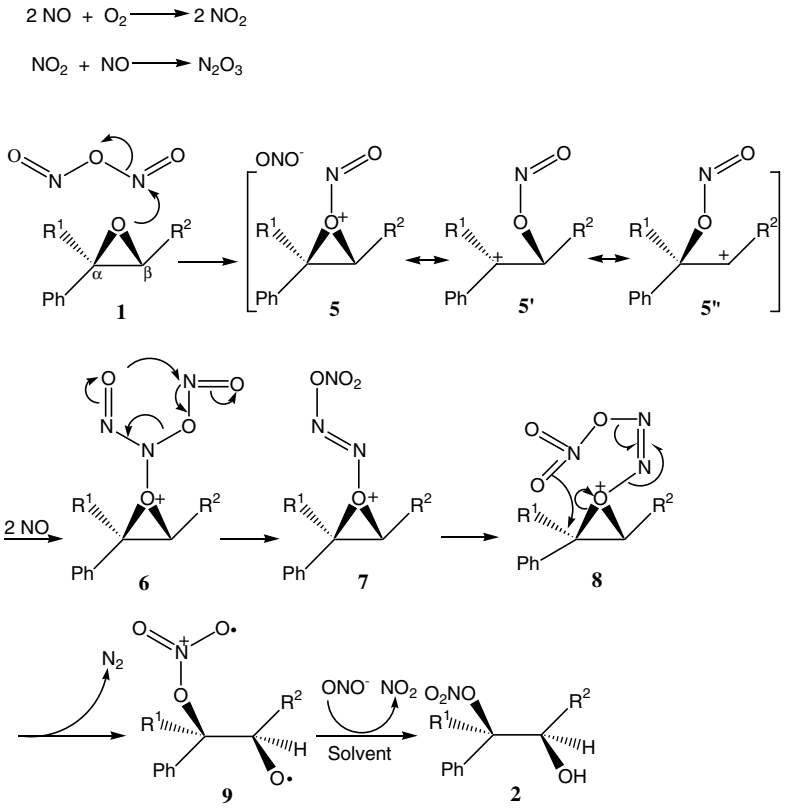
A proposed mechanism is depicted in Scheme 1. It appears that a trace of O_2 retained in reaction system plays a key role in the initiation of reactions under consideration. NO is readily oxidized to NO_2 and then converted into N_2O_3. Displacement of the good leaving group nitrite (–ONO) from N_2O_3 by the Lewis basic oxygen of epoxide leads to form **5**. Resonance forms **5**, **5′**, and **5″** (Scheme 1) will contribute unequally to the real structure of carbocation intermediate generated from the reaction of **1** with N_2O_3. Among them, **5** is considered to be the most stable and dominant resonance form. It is also rationalized by the formation of major products (Table 1) produced by following the mechanism illustrated in Scheme 1 starting with **5**. Addition of 2 equiv of NO to the *O*-nitroso group of **5** gives **6**, which rearranges to **7**.[1c] Compound **7** in turn undergoes intra-

Table 2. Reduction of nitrates **2**



Entry	1,2-Glycol	Reductant	Reaction time (h)	Yield[a] (%)	Configuration (glycol/epoxide)	ee[b] (%)	dr[c] (%)
1	**4a**	NH_2NH_2	120	74.8	(*R*,*R*)[d]/(*R*,*R*)[d]	—	—
2	**4a**	$NaBH_4$	24	0	—/(*R*,*R*)[d]	—	—
3	**4a**	$LiAlH_4$	4	85.4	(*R*,*R*)[d]/(*R*,*R*)[d]	95.4	86:1
4	**4a**	$(NH_4)_2S$	2	>99	(*R*,*R*)[d]/(*R*,*R*)[d]	>99	>99:1
5	**4c**	rt	24	95.0	(*R*,*R*)[d]/(*R*,*R*)[d]	>99	>99:1
6	**4d**	$(NH_4)_2S$	0.5	98.5	(*R*,*R*)[d]/(*R*,*R*)[d]	90.7	12:1
7	**4e**	$(NH_4)_2S$	2	67.3	(*R*,*R*)[d]/(*R*,*R*)[d]	95.7	12:1
8	**4f**	$(NH_4)_2S$	0.7	>99	(2*S*,3*R*)[e]/(2*S*,3*R*)[d]	87.9	37:1
9	**4g**	$(NH_4)_2S$	1.5	92.3	(*R*,*R*)[e]/(*R*,*R*)	93.6	13.4:1
10	**4h**	$(NH_4)_2S$	2	91.0	(2*S*,3*R*)[e]/(2*S*,3*R*)[d]	93.9	60:1

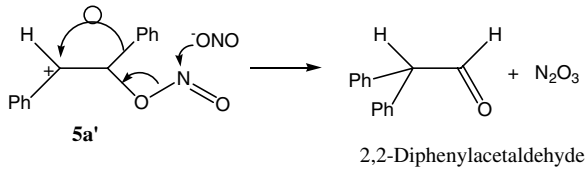
[a] Isolated yield after silica gel chromatography.
[b] Values for ee were determined by chiral HPLC.
[c] Values for dr were determined by chiral HPLC.
[d] The absolute configurations were determined by comparing the measured optical rotations with those reported.
[e] The absolute configuration were tentatively assumed by analogy *syn*-ring opening reaction mode.



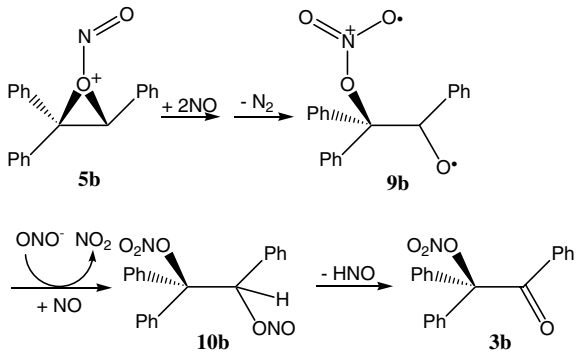
Scheme 1. Mechanism for the ring opening of epoxides.

molecular nucleophilic substitution to form **9**. Such a front side approach causes the retention of configuration. The resulting **9** undergoes electron transfer with –ONO and H-abstraction from solvent molecules to generate nitrate **2**. In species **5**, most of the positive charge will reside at the α-site because the positive charged carbon will be resonance-stabilized by the phenyl group. Therefore, the β-carbon–oxygen bond will be longer and weaker than the other and will be the major bond being broken by the addition of a nucleophile.

In the case of **1a**, the formation of by-product 2,2-diphenylacetaldehyde in a yield of 20% involves a mechanism in which less stable resonance form **5a′** undergoes a rearrangement like the pinacol rearrangement induced by a nucleophilic attack of ONO^- at nitrogen atom to generate by-product 2,2-diphenylacetaldehyde (Scheme 2). However, in the case of **1b**, a rearrangement from a stable tertiary carbocation **5b′** may be thermodynamically unfavorable. Another reason for it may be due to the spatial factor caused by two phenyl groups at the α-carbon in the rearrangement of **5b′**. Hence, resonance form **5b** undergoes a process indicated in Scheme 3 to give **3b**.[2b,21] Thus, the formation of 2,2-diphenylacetaldehyde and **3b** provides unambiguous evidence for supporting the mechanism suggested in Scheme 1 involving a cationic intermediate **5**.



Scheme 2.



Scheme 3.

These findings of research have allowed the author to reach a conclusion at the reaction of enantiopure epoxides with NO, which leads to a *syn*-ring opening and to the production of single *erythro*-β-hydroxy nitrates with the retention of configuration. The resulting nitrates will be easily converted into other vicinal difunctionalized compounds. Problems remained in this study are that the reaction occurred within a time span of 3–5 days.

Acknowledgment

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14. *Representative procedure for the reaction of epoxides with NO*: A stock solution was prepared by dissolving 1.16 mmol of **1a** (216 mg) in 80 mL of anhydrous CH_2Cl_2. The stock solution was previously deaerated with argon for 15 min.[22] In the course of degassing, the argon flow rate was controlled by regulating the flow meter at 0.8 L min^{-1} and the stock solution was kept at a pressure of up to +10 mm H_2O over local atmospheric pressure at room temperature. NO was produced by the reaction of 1 M H_2SO_4 solution with saturated $NaNO_2$ aqueous solution under an argon atmosphere, in which the sulfuric acid was added dropwise. NO was carried by argon and purified by passing it through a series of scrubbing bottles containing distilled water, 4 M NaOH, $CaCl_2$ in this order. Purified NO was bubbled through the stock solution until the completion of reaction, as indicated by TLC. The solution was then concentrated under vacuum and purified by column chromatography on silica gel to give 228 mg of **2a** (80% yield) as white crystallines. *Data for* **2a**: white crystal, $[\alpha]_D^{22}$ +39 (*c* 0.48, EtOH), mp 96–98 °C; $R_f = 0.3$ [EtOAc/*n*-hexane, 1:10, v/v, silica gel plate]; IR (KBr) ν_{max} 3454 (OH), 1632 (NO_2), 1277 (NO_2), 880 (ON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.21 (m, 6H), 7.11–7.09 (m, 4H), 5.88 (d, $J = 8.4$ Hz, 1H), 4.96 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 134.3, 129.1, 128.5, 128.3, 127.3, 127.1, 88.9 (CH–ONO_2), 75.7 (CH–OH); MS (EI, 70 eV) *m*/*z* (%) 197 (M–ONO_2, 1.9), 182 (4.0), 167 (9.1), 107 (100.0), 77 (59.6). Anal. Calcd (%) for $C_{14}H_{13}NO_4$ (259): C, 64.86; H, 5.02; N, 5.41. Found: C, 64.59; H, 4.64; N, 5.42.
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20. *Representative procedure for the reduction of* β*-hydroxy nitrates with* $(NH_4)_2S$:[19a] 53 mg (0.20 mmol) of **2a** was treated with 1 mL of aqueous solution containing a vast excess of ammonium sulfide (corresponding to 8% free sulfur) and 2 mL of ethanol. The treatment was accompanied by a color change to orange and by the precipitation of sulfur. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with 10 mL of water and extracted with 3×15 mL of ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, filtered, and then concentrated. The product was purified by flash chromatography on silica gel, affording 44 mg of **4a** (>99% yield) as white crystallines. *Data for* **4a**: white crystal, $[\alpha]_D^{22}$ +86 (*c* 0.9, EtOH) [lit.,[22] $[\alpha]_D^{21}$ +91 (*c*, 1.1, EtOH)]; mp 136–138 °C; $R_f = 0.2$ [ethyl acetate/*n*-hexane, 1:3, v/v, silica gel plate]; IR (KBr) ν_{max} 3393 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 6H), 7.14–7.11 (m, 4H), 4.71 (d, $J = 2.4$ Hz, 2H), 2.92 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 128.1, 127.9, 126.9, 79.1 (CH); MS (EI, 70 eV) *m*/*z* (%) 214 (M^+, 0.4), 165 (1.3), 152 (0.7), 107 (100.0); ee >99%, dr >99:1 [HPLC, Chiralcel OJ-H column, hexane/2-propanol, 90:10, v/v, the flow rate, 0.8 mL/min].
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