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Chemo- and regioselective ring-opening of donor–acceptor oxiranes with *N*-heteroaromatics†

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The first ring-opening of D–A oxiranes with *N*-heteroaromatics in a chemoselective C–C bond cleavage manner was achieved. In the presence of 5 mol% of $Y(OTf)_3$ as the catalyst, diverse *N*-heteroaromatics, including benzotriazoles, purines, substituted benzimidazole, imidazole and pyrazole, reacted well with various D–A oxiranes, providing acyclic nucleoside analogues containing a *N*-glycosidic bond in up to 97% yield and up to >95 : 5 regioselectivity. Through simple transformation, the Ganciclovir analogue could also be obtained.

Donor–acceptor (D–A) oxiranes are exceptionally useful three-atom building blocks owing to their versatility in organic synthesis.[1] In recent years, the [3+2] cycloaddition of D–A oxiranes with various dipolarphiles (C=C, C=O, C=N, C≡C, C≡N) has been elegantly conducted by the groups of Zhang, Feng, Zhong, and others (Scheme 1a).[2–5] However, in sharp contrast, the ring-opening reaction of D–A oxiranes has scarcely been reported in the literature (Scheme 1b). In 2017, Pan and co-workers pioneered the ring-opening of D–A oxiranes with γ-hydroxyenones using $Sc(OTf)_3$ as the catalyst for the synthesis of 2,5-disubstituted furans, in which a chemoselective C–O bond cleavage of oxiranes was reported.[6] To the best of our knowledge, the ring-opening of D–A oxiranes with a chemoselective C–C bond cleavage has not been reported to date. Therefore, developing a ring-opening of D–A oxiranes with a C–C bond cleavage in a chemoselective manner is highly desirable.

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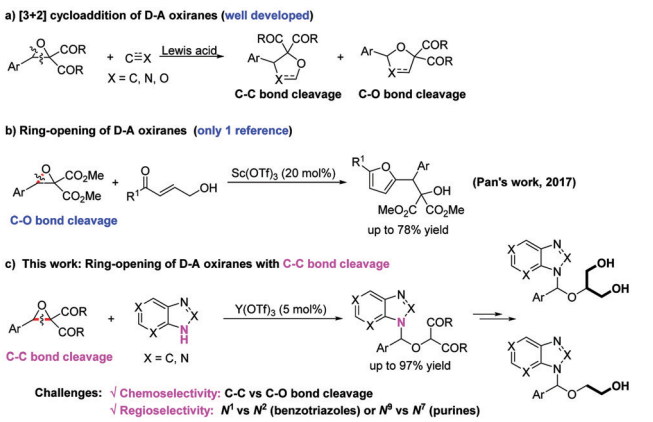
Benzotriazole and purine derived acyclic nucleosides, containing *N*-glycosidic bonds, have displayed significant bioactivities and representative examples are shown in Fig. 1.[7] Benzotriazole **I** exhibits an antileishmanial activity.[8] Acyclovir and Ganciclovir have been approved by the FDA to treat herpes and cytomegalovirus (CMV), respectively (Fig. 1a).[9] Due to the existence of two tautomeric forms for benzotriazole and purines (Fig. 1b), the construction of corresponding acyclic nucleosides might face the challenge of regioselectivity. In this work, we envisage realizing the ring-opening of D–A oxiranes with a chemoselective C–C bond cleavage by changing the Lewis acid catalyst and its coordination mode. Herein, we report a $Y(OTf)_3$-catalyzed ring-opening of D–A oxiranes to *N*-heteroaromatics with a C–C bond cleavage, affording diverse acyclic nucleoside analogues containing a *N*-glycosidic bond in a chemo- and regioselective manner, which could be derived into Ganciclovir analogues (Scheme 1c).

Initially, the reaction of benzotriazole **1a** with D–A oxirane **2a** was selected as the model reaction (Table 1). With $Sc(OTf)_3$ as the Lewis acid catalyst, the ring-opening reaction occurred and it did encounter the challenge chemoselectivity and



Scheme 1 Profile of D–A oxiranes with cycloaddition or ring-opening.

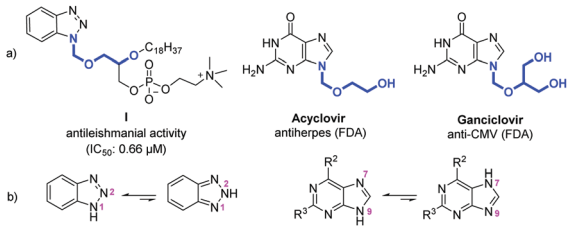
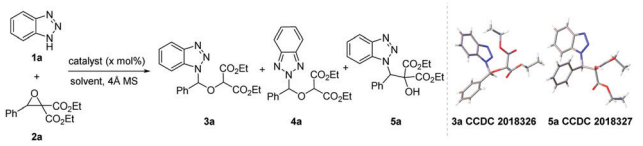


Fig. 1 (a) Examples of bioactive acyclic nucleoside analogues; (b) tautomers of benzotriazole and purines.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	X	Solvent	T (°C)	t (h)	Yield[b] (%)	Ratio[c] (3a/4a/5a)
1	$Sc(OTf)_3$	5	$PhCH_3$	40	24	6	45 : 23 : 32
2	$Yb(OTf)_3$	5	$PhCH_3$	40	24	18	21 : 18 : 61
3	$BF_3{\cdot}Et_2O$	5	$PhCH_3$	40	24	N.R.	—
4	$Cu(OTf)_2$	5	$PhCH_3$	40	24	N.R.	—
5	$Gd(OTf)_3$	5	$PhCH_3$	40	24	18	29 : 30 : 41
6	$Er(OTf)_3$	5	$PhCH_3$	40	24	19	24 : 25 : 51
7	$Y(OTf)_3$	5	$PhCH_3$	40	24	29	19 : 30 : 51
8	$Y(OTf)_3$	5	THF	40	24	10	40 : 13 : 47
9	$Y(OTf)_3$	5	$CHCl_3$	40	24	20	40 : 40 : 20
10	$Y(OTf)_3$	5	DCM	40	24	28	45 : 33 : 22
11	$Y(OTf)_3$	5	DCE	40	24	61	57 : 33 : 10
12	$Y(OTf)_3$	5	DCE	rt	24	Trace	—
13	$Y(OTf)_3$	5	DCE	60	24	70	71 : 24 : 5
14	$Y(OTf)_3$	5	DCE	80	10	99(94)[d]	96 : 4 : 0
15	$Y(OTf)_3$	3	DCE	80	24	36	67 : 28 : 5
16	$Y(OTf)_3$	10	DCE	80	10	88	95 : 4 : 1
17	—	—	DCE	80	10	N.R.	—
18[e]	$Y(OTf)_3$	5	DCE	80	10	N.R.	—
19[f]	$Y(OTf)_3$	5	DCE	80	10	11	65 : 16 : 19

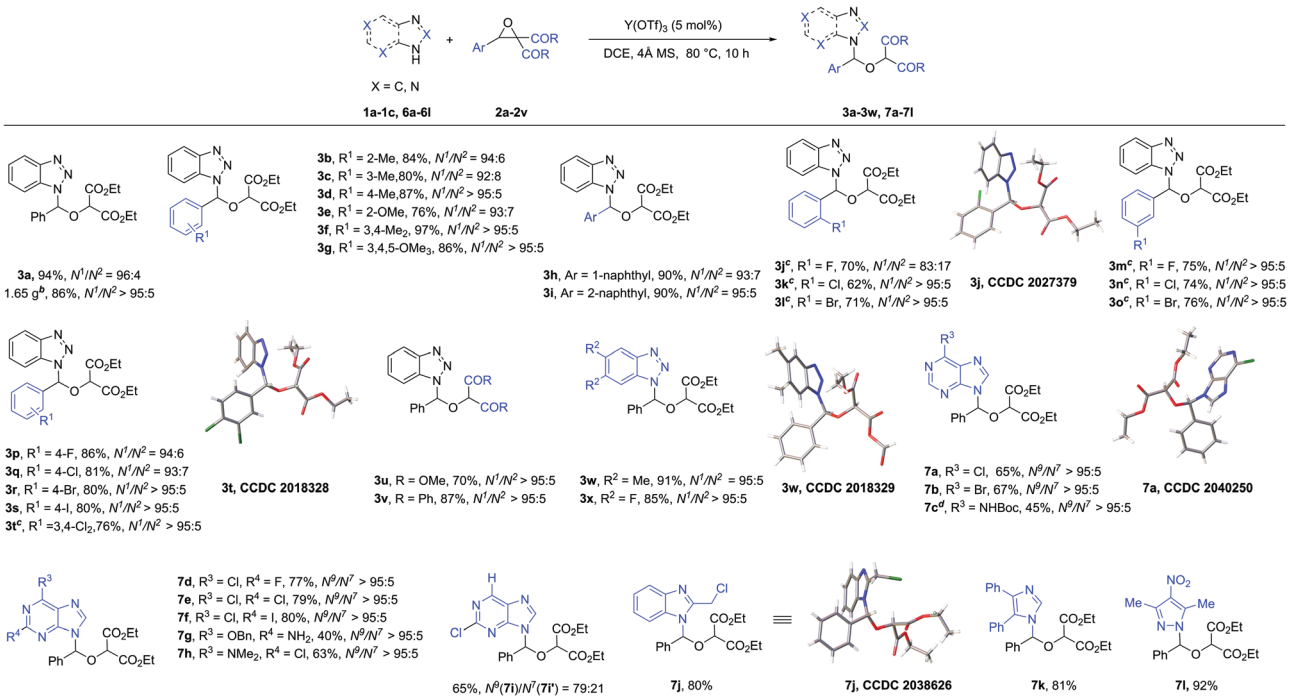
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $Y(OTf)_3$ (5 mol%), 4 Å MS (30 mg) and DCE (2 mL) at 80 °C for 10 h. [b] The total yield was determined by ^1H NMR using CH_2Br_2 as an internal standard. [c] The ratio was determined by ^1H NMR analysis of crude product. [d] Isolated yield of **3a** in parentheses. [e] Without 4 Å MS. [f] H_2O (10 μL) was added.

regioselectivity, affording a mixture of N^1 alkylated with C–C bond cleavage product **3a**, N^2 alkylated with C–C bond cleavage product **4a**, and N^1 alkylated with C–O bond cleavage product **5a** (entry 1). Then, different Lewis acids were evaluated and $Y(OTf)_3$ was determined as the optimal catalyst, delivering three ring-opening products in a 29% total yield, in which the C–O bond cleavage product **5a** was the major isomer (entries 2–7). Several solvents were examined, and DCE could give a higher total yield of 61%, in which the C–C bond cleavage product **3a** was the major one (entries 6–11). The screening of temperature showed that increasing the temperature was favor to the total yield and the formation of N^1 alkylated product **3a**. Further studies indicated that N^2 alkylated product **4a** could convert into product **3a** at high temperature and catalytic conditions (see ESI† for details). It was proposed that N^1 alkylated product **3a** was a thermodynamic product, while N^2 alkylated product **4a** was a kinetic product. At 80 °C, the ring-opening products were given in 99% total yield, and the ratio of **3a**/**4a**/**5a** reached into 96/4/0 (entries 12–14). Evaluation of the catalyst loading showed that 5 mol% of $Y(OTf)_3$ was optimal (entries 14–16). It should be noted that the reaction did not happen without $Y(OTf)_3$ or 4 Å MS (entries 17 and 18). When H_2O was added, only 11% total yield was observed (entry 19), indicating that the function of 4 Å MS might be to scavenge adventitious water.

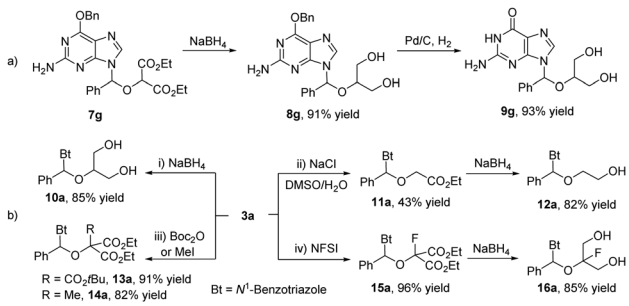
Under the optimized reaction conditions (Table 1, entry 14), the substrate scope of D–A oxiranes was evaluated (Scheme 2). For oxiranes **2b**–**2g** bearing electron-rich substituents at the aryl moieties, the adducts **3b**–**3g** were afforded in 76–97% yields and 92 : 8 to > 95 : 5 regioselectivities. 1-Naphthyl and 2-naphthyl substituted oxiranes **2h**–**2i** were also suitable reactants. For oxiranes **2j**–**2t** with different halogen groups at the aryl fragments, the ring-opening products **3j**–**3t** were given in 62–86% yields and 83 : 17 to > 95 : 5 regioselectivities. In the case of strongly electron-withdrawing group at the aryl moieties, such as 4-CF_3 or 4-NO_2 group, the reactions did not occur. As for diethyl (*E*)-3-styryloxirane-2,2-dicarboxylate, the reaction was complex (see ESI† for details). When D–A oxiranes **2u**–**2v** with methyl ester or benzoyl substituent group were employed, the adducts **3u**–**3v** were obtained in good results. In addition, 5 mmol of benzotriazole **1a** reacted smoothly with D–A oxirane **2a**, affording 1.65 g (86% yield) of the adduct **3a** with > 95 : 5 regioselectivity. It should be emphasized that the ring-opening reaction of D–A oxiranes proceeded in a chemoselective manner with C–C bond cleavage.

Subsequently, the substrate scope of *N*-heteroaromatics was explored. 5,6-Dimethylbenzotriazole **1b** and 5,6-difluorobenzotriazole **1c** were also suitable reactants to form the adducts **3w**–**3x**. A series of substituted purines **6a**–**6h** with halogen, amino, or alkoxy substituents at C2 or C6 position were examined, the corresponding acyclic nucleoside analogues **7a**–**7h** were obtained in a regioselective manner with 40–80% yields. In the case of 6-hydrogen purine **6i**, a mixture of N^9 adduct and N^7 adduct was obtained. These results showed that the N^9/N^7 regioselectivity was greatly affected by the steric hindrance of the substituent group at the C6 position of purine. Then, substituted benzimidazole **6j**, imidazole **6k**, and pyrazole **6l** were used, the ring-opening smoothly afforded the adducts **7j**–**7l** in 80–92% yields.

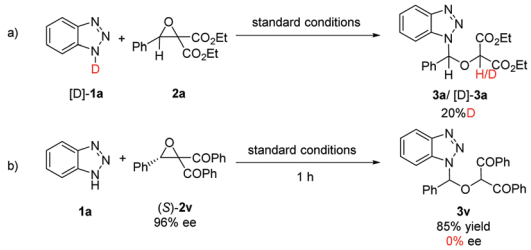
The synthetic transformations of the ring-opening adducts were then performed (Scheme 3). Acyclic nucleoside analogue **7g** could be easily reduced to afford acyclic nucleoside **8g** bearing two hydroxymethyl groups in 91% yield. Through further debenzylation, the acyclic nucleoside **9g** was obtained (Scheme 3a). It should be noted that the acyclic nucleoside **9g** was an analogue of Ganciclovir, in which a phenyl group was linked at the C1′-position of the side chain in Ganciclovir. By simple reduction, acyclic product **10a** with two vicinal hydroxymethyl groups was obtained in 85% yield (Scheme 3b-i). Through Krapcho decarboxylation, the acyclic product **11a** bearing one ester group was given in 43% yield, which could be reduced into acyclic nucleoside analogue **12a** in 82% yield (Scheme 3b-ii). By treatment of Boc_2O or MeI, the corresponding products **13a** containing three ester groups and **14a** bearing a methyl group could be generated, respectively



Scheme 2 Substrate scope[a]. [a] **1a–1c** for benzotriazoles, **6a–6i** for purines, **6j–6k** for substituted imidazoles, **6l** for substituted pyrazole. Unless otherwise noted, the reaction conditions were: **1** or **6** (0.1 mmol), **2** (0.1 mmol), $Y(OTf)_3$ (5 mol%), 4 Å MS (30 mg) and DCE (2 mL) at 80 °C for 10 h. All yields are isolated. The ratio of N^1/N^2 and N^7/N^9 were determined by ^1H NMR analysis of the crude reaction mixture. [b] 5.0 mmol scale. [c] At 100 °C. [d] **6c** is *N,N*-Di*tert*-butoxycarbonyl-9*H*-purin-6-amine.



Scheme 3 Transformation of the ring-opening products.



Scheme 4 Experimental mechanistic studies.

(Scheme 3b-iii). A fluorine atom could also be introduced into the acyclic side chain to form product **15a** in 96% yield, which could deliver fluorine-containing acyclic nucleoside analogue **16a** with two vicinal hydroxymethyl groups by simple reduction (Scheme 3b-iv).

In order to gain insight into the mechanism, isotopic-labeling experiment was performed with [D]benzotriazole and D–A oxirane **2a**.[10] Deuterium incorporation was only observed at the α-position of the ester group (Scheme 4a). The reason for the low deuteration rate might be that the water adsorbed in 4 Å MS participated in the H-transfer step (see ESI† for details). With enantioenriched (*S*)-**2v** as the reactant,[11] the ring-opening reaction with benzotriazole **1a** was evaluated under optimized conditions. However, the desired ring-opening adduct **3v** was obtained in a racemic form (Scheme 4b). Besides, the electronic conductivity for the mixture of D–A oxirane **2a** with $Y(OTf)_3$ was tracked in the reaction with 0.200 μS cm^{-1} (see ESI† for details). These experiment indicated that in the presence of $Y(OTf)_3$, the oxirane first underwent C–C bond cleavage to form a zwitterionic intermediate, which further react with nucleophilic benzotriazole to afford ring-opening adduct **3v**.

The Hammett study was carried out on different D–A oxiranes bearing *meta*-substituent in the aryl moiety. The negative slope (−2.997) indicated that the smaller the electron dispersion from the benzylic carbon of D–A oxirane, the faster the reaction. These studies showed that the reaction might proceed *via* a carbocation intermediate. The kinetic order of each reaction component was determined through studying initial rates of the reaction. The rate shows that a zero-order dependence on the concentration of **1a**, while approximately first-order dependence on the concentration of **2a** and catalyst $Y(OTf)_3$ (see ESI† for details). These data

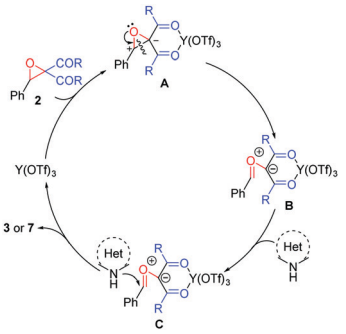
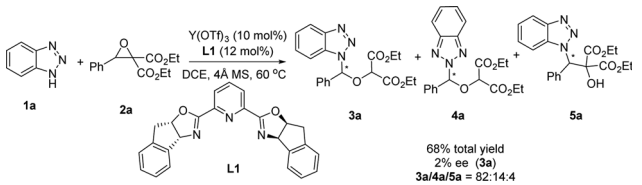


Fig. 2 Proposed mechanism.



Scheme 5 Catalytic asymmetric ring-opening reaction.

indicated that the coordination of **2a** and $Y(OTf)_3$ might be involved in the rate-determining step.

On the basis of our experimental results and previous reports, a possible mechanism was proposed in Fig. 2. First, D–A oxirane **2** is activated by $Y(OTf)_3$ *via* coordination with the geminal bisketone moiety to form the intermediate **A**. Then, the direct C–C bond cleavage of intermediate **A** will generate a zwitterion, in which a carbocation at the benzyl position was involved. After that, a metal-coordinated carbonyl ylide **B** was formed. Finally, the nucleophilic attack of *N*-heteroaromatics to carbonyl ylide **B** generated the desired ring-opening adducts and released $Y(OTf)_3$.

Furthermore, the enantioselective variant of this ring-opening reaction was tried (Scheme 5). A series of Lewis acids and chiral oxazoline ligands were screened (see ESI† for details). With $Y(OTf)_3$-**L1** as the catalyst, the ring-opening adducts were obtained in 68% total yield, along with 2% ee for N^1 alkylated product **3a**.

In summary, we reported the first ring-opening of D–A oxiranes with *N*-heteroaromatics in a chemoselective C–C bond cleavage manner. With 5 mol% of $Y(OTf)_3$ as the catalyst, a variety of *N*-heteroaromatics, including benzotriazoles, purines, substituted benzimidazole, imidazole and pyrazole, reacted well with diverse D–A oxiranes, providing ring-opening adducts containing a *N*-glycosidic bond in 40–97% yields and 79 : 21 to >95 : 5 regioselectivities. Furthermore, diverse acyclic nucleoside analogues could be afforded from the ring-opening adducts through simple derivatization. This methodology may provide a practical route to construct acyclic nucleosides and Ganciclovir analogues.

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Conflicts of interest

There are no conflicts to declare.

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