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Asymmetric H_2O-Nucleophilic Ring Opening of D−A Cyclopropanes: Catalyst Serves as a Source of Water

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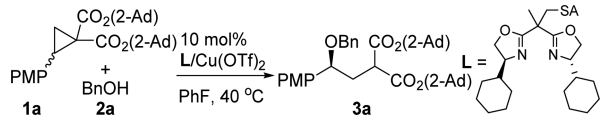
Supporting Information

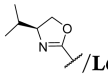
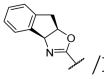
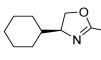
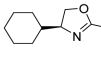
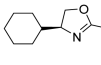
ABSTRACT: The first catalytic enantioselective ring-opening reaction of donor−acceptor cyclopropanes with water is described. By employing Cy-TOX/Cu(II) as catalyst, the reaction performed very well over a broad range of substrates, leading to the ring-opening products in 70−96% yields with up to 95% ee under mild conditions. The current method provides a new approach to direct access to γ-substituted GBH derivatives very efficiently. Importantly, $Cu(ClO_4)_2·6H_2O$ proves to serve as both a Lewis acid and a source of water, which affords a fine system to controllably release water as a nucleophile in the asymmetric catalysis.

Owing to their flexible reaction patterns and versatile approaches for further elaboration of the products, donor−acceptor (D−A) cyclopropanes are considered as useful synthetic building blocks and have attracted increasing attention of synthetic chemists in recent years.[1] Asymmetric ring-opening annulations[2] have been well studied and successfully applied in the total synthesis of natural products and biologically active molecules.[3] Many reports on the direct nucleophilic ring-opening reactions of D−A cyclopropanes have appeared,[2−4] however, no successful examples on their asymmetric versions are described except for the enantioselective ring-opening reactions of D−A cyclopropanes with secondary amines and indoles.[5] In our ongoing research on the asymmetric ring-opening of D−A cyclopropanes, we are interested in developing an asymmetric reaction of H_2O[6] with D−A cyclopropanes, a potential approach to optically active GHB acid derivatives.[7] In the past several years, this proves very challenging since water is a weak nucleophile and the corresponding product alcohol is more nucleophilic than water, which leads to competing byproducts in the ring-opening reaction. In addition, water in the reaction system can normally poison the Lewis acid catalyst and slow down the reaction.[8] Here, we report a novel strategy by employing catalyst as a source of water to realize the asymmetric ring-opening reactions of D−A cyclopropanes with water.

Initially, we tried several Lewis acids as catalysts for the water ring-opening reaction of D−A cyclopropane **1a** but failed. In order to shed light on this reaction, we chose alcohol as a model substrate instead of water for the initial study. We employed In-TOX/$Ni(ClO_4)_2$ as the catalyst, which is optimal in the reaction of amine with D−A cyclopropane **1a**, and tested 5.0 equiv of benzyl alcohol **2a** as nucleophile instead of amine to run the ring-opening reaction under the standard conditions. Unfortunately, the desired product was not observed. Thus, we turned to other catalyst systems and found that $Cu(OTf)_2$/bisoxazoline (BOX) could promote this reaction (Table 1). After optimizing the solvents, Lewis acids, and the ester groups, we screened various BOX ligands and found that Cy-BOX **L1** gave 80% ee in 87% yield (entry 1). Further study showed the side arm (SA) on the bridge carbon of BOX also influenced the results.

Table 1. Optimization of Reaction Conditions[a]



entry	SA/**L**	T(°C)	yield(%)[b]	ee (%)[c]
1	H/**L1**	40	87	80
2	Ph/**L2**	40	81	84
3	3,5-^{t}Bu$_2$C$_6$H$_3$/**L3**	40	65	82
4	3,5-$(OCH_3)_2C_6H_3$/**L4**	40	82	86
5	3,4,5-$(OCH_3)_3C_6H_3$/**L5**	40	74	81
6	 /**L6**	40	82	87
7	 /**L7**	40	89	85
8	 /**L8**	40	88	89
9	 /**L8**	0	87	93
10[d]	 /**L8**	0	90	93

[a]Under Ar atmosphere, **1a** (0.44 mmol), **2a** (0.20 mmol), $Cu(OTf)_2$ (0.020 mmol), **L** (0.024 mmol) in C_6H_5F (2.0 mL) and 4 Å MS (200 mg). [b]Isolated yield based on **2a**. [c]Determined by chiral HPLC. [d]In C_6H_5F (0.4 mL) and 4 Å MS (40 mg).

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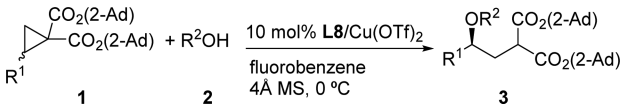
As shown in Table 1, 84% ee could be obtained by installing phenyl as a SA (entry 2), and substituted phenyl further improved the enantiomeric excess to 87% (entries 3–7). Finally, cyclohexyl-trisoxazoline[9,10] (Cy-TOX) **L8** was found to give the optimal result. In this case, the desired ring-opening product **3a** was obtained in 88% yield, with 89% ee in the presence of 10 mol % **L8**/$Cu(OTf)_2$ (entry 8). Lowering the reaction temperature to 0 °C, combined with increasing the substrate concentration, the desired product resulted in 90% yield with 93% ee (entry 10).

The current catalyst system was found insensitive to the structure of the nucleophiles. When the reactions were performed using benzyl alcohol **2a**, the reaction proceeded smoothly to furnish product **3a**–**3c** in high yields with good to excellent levels of enantioselectivity (90–96% ee, Table 2, entries 1–3), not only for the cyclopropanes with both electron-donating and -withdrawing groups on the phenyl substituents but also for those substituted with 2-thienyl groups, which are flexible for further transformation in organic synthesis. Since the benzyl group could be readily removed, this process provided a synthetically useful approach to a variety of enantio-enriched substituted GHB diesters. Unsaturated alcohols, such as cinnamyl alcohol and propargyl alcohol, both reacted with high enantioselectivity (93–94% ee, entries 4–5). The reaction also worked well with 1-octanol **2d**, giving the target product **3f** in 79% yield with 94% ee (entry 6). Functionalized alcohol **2e** derived from ethylene glycol was well-tolerated in the current system, affording the corresponding γ-alkoxy butyric diester **3g** in 73% yield with 93% ee (entry 7). In particular, the ring opening with secondary alcohol **2f** proceeded very well, providing the desired product **3h** in 80% yield with 94% ee (entry 8).

Table 2. Substate Scope using Alcohol as Nucleophile[a]

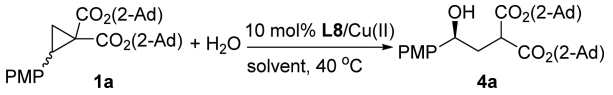


entry	R^1	R^2 (2)	3/yield (%)[b]	ee (%)[c]
1	4-$MeOC_6H_4$	Bn (**2a**)	**3a**/90	93
2[d]	4-BrC_6H_4	Bn (**2a**)	**3b**/89	96
3	2-thienyl	Bn (**2a**)	**3c**/92	90
4	4-$MeOC_6H_4$	cinnamyl (**2b**)	**3d**/92	94
5	4-$MeOC_6H_4$	propargyl (**2c**)	**3e**/70	93
6	4-$MeOC_6H_4$	*n*-octyl (**2d**)	**3f**/79	94
7	4-$MeOC_6H_4$	$TBSOCH_2CH_2$ (**2e**)	**3g**/73	93
8	4-$MeOC_6H_4$	^{i}Pr (**2f**)	**3h**/80	94

[a]Conditions: All reactions were carried out under Ar atmosphere at 0 °C, **1** (0.44 mmol), **2** (0.20 mmol), $Cu(OTf)_2$ (0.020 mmol), **L8** (0.024 mmol) in C_6H_5F (0.4 mL) and 4 Å MS (40 mg). [b]Isolated yield based on **2**. [c]Determined by chiral HPLC. [d]At 40 °C.

Inspired by the success of the asymmetric ring-opening reaction with alcohol, we next reinvestigated water as nucleophile in an effort to obtain the corresponding GHB diesters directly. We employed $Cu(OTf)_2$/**L8** as the catalyst and treated racemic D–A cyclopropane **1a** with 5.0 equiv of water as nucleophile in fluorobenzene at 40 °C. Fortunately, the ring-opening product **4a** was obtained with 89% ee but in only 9% yield (entry 1, Table 3). As tabulated in Table 3, the solvents influence the reaction strongly. For example, the reaction did not occur in toluene (entry 2). When THF was used, the yield was improved to 29% (entry 3). With dimethoxyethane (DME, containing 230 ppm of water) as solvent, the desired product **4a** was afforded in 23% yield with 92% ee (entry 4).

Table 3. Optimization of Reaction Conditions[a]

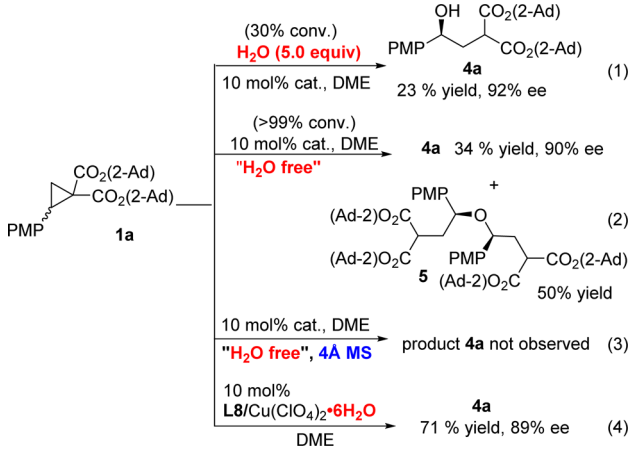


entry	Cu(II)	solvent	water (equiv)	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	PhF	5.0	9	89
2	$Cu(OTf)_2$	PhMe	5.0	–	–
3	$Cu(OTf)_2$	THF	5.0	29	91
4	$Cu(OTf)_2$	DME	5.0	23	92
5	$Cu(ClO_4)_2{\cdot}6H_2O$	DME	0	71	89
6[d]	$Cu(ClO_4)_2{\cdot}6H_2O$	DME	0	57	90
7[e]	$Cu(ClO_4)_2{\cdot}6H_2O$	DME	0	92	90
8[e,f]	$Cu(ClO_4)_2{\cdot}6H_2O$	DME	0	95	93
9[g]	$Cu(ClO_4)_2{\cdot}6H_2O$	DME	0	0	–

[a]Under Ar atmosphere, **1a** (0.20 mmol), metal (0.020 mmol), **L8** (0.024 mmol) in solvent (1.0 mL). [b]Isolated yield based on **1a**. [c]Determined by chiral HPLC. [d]With 5 mol % catalyst. [e]With 15 mol % catalyst, in 2.0 mL of DME. [f]At room temperature. [g]4 Å MS (200 mg).

Remarkably, it was found that the amount of water in this reaction proved critical (Scheme 1). When it was conducted without additional water, the reaction could also occur, affording the product **4a** in 34% yield with 90% ee (Scheme 1, eq 2). In this case, the D–A cyclopropane **1a** was all consumed, and a product-initiated nucleophilic ring-opening byproduct **5** was isolated as a main byproduct. These results suggested that product **4a** can further nucleophilic attack the D–A cyclopropane **1a** even faster than water in the reaction system, which is a major competitor of water for the ring-opening process and will destroy the desired product **4a**. We struggled to improve the yield and found that the reaction was sluggish with an additional 5.0 equiv of water. Only 23% yield was obtained with a big surplus of cyclopropane, and no byproduct was detected, probably due to the reason that the excessive amount of water poisoned the Lewis acid and deteriorated the effective activation of the D–A cyclopropane (eq 1). We also tested the addition of 4 Å molecule sieves to remove the water in the system, but it led to no reaction (eq 3). Hundreds of attempts failed, and higher than 40% yields proved to be a challenging task. As the amount of water affected the reaction clearly, we conceived that keeping the water at a proper concentration may suppress both the competing coordination

Scheme 1. Effects of the Water Loading



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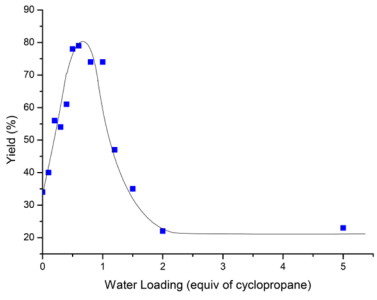
and the undesired alcohol nucleophilic ring-opening reaction. Further screening carefully on the water loading (Figure 1, for



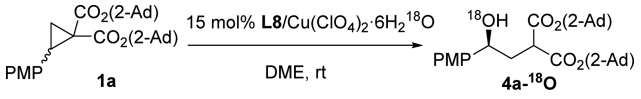
x	y	x	y	x	y
0	34	0.5	78	1.5	35
0.1	40	0.6	79	2.0	22
0.2	56	0.8	74	5.0	23
0.3	54	1.0	74		
0.4	61	1.2	47		

x = water loading (eq.)
y = yield of **4a** (%)

Figure 1. Relationship of Yield and Water Loading. Conditions: All reactions were carried out under Ar atmosphere at 40 °C, **1a** (0.20 mmol), $Cu(OTf)_2$ (0.020 mmol), **L8** (0.024 mmol), $[\mathbf{1a}]_0$ = 0.20 M in DME (1.0 mL), isolated yield based on **1a**.

details, see SI) revealed that the yield of **4a** could reach a slightly varied level in a range of 74−78%, with the ee values remaining in 91−92% when the water was added in a range of 0.5−1.0 equiv.[12] However, the protocol by direct adding water to the reaction system suffered a major setback due to the inconvenient experimental operation and the unreproducible yields. Inspired by these results, we tested a crystalline hydrate of catalyst as a reservoir to control and release water. It was found that the product **4a** was furnished in 71% yield with 89% ee (entry 5, Table 3; eq 4, Scheme 1) when $Cu(ClO_4)_2{\cdot}6H_2O$ was employed. Although 5 mol % of the $Cu(ClO_4)_2{\cdot}6H_2O$ could lead to 57% yield (entry 6), 15 mol % of the $Cu(ClO_4)_2{\cdot}6H_2O$ gave the desired product in 92% yield and 90% ee (entry 7). Further lowering the reaction temperature from 40 to 25 °C, the yield was improved to 95% with 93% ee (entry 8) in the case of **L8**/$Cu(ClO_4)_2{\cdot}6H_2O$ as the catalyst. In the presence of 4 Å MS, the desired product was not observed (entry 9).

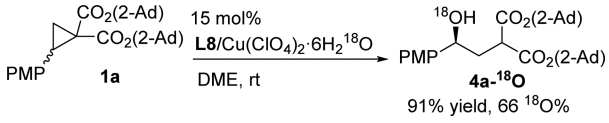
In order to trace the source of the hydroxyl oxygen in the ring-opening product, an isotropic labeling experiment was conducted by using $Cu(ClO_4)_2{\cdot}6H_2{}^{18}O$ instead of $Cu(ClO_4)_2{\cdot}6H_2O$. As expected, 66 ^{18}O% of the **4a-^{18}O** was obtained.[11] This result demonstrated that $Cu(ClO_4)_2{\cdot}6H_2O$ plays dual roles both as the catalyst and a source of water for the ring-opening reaction.



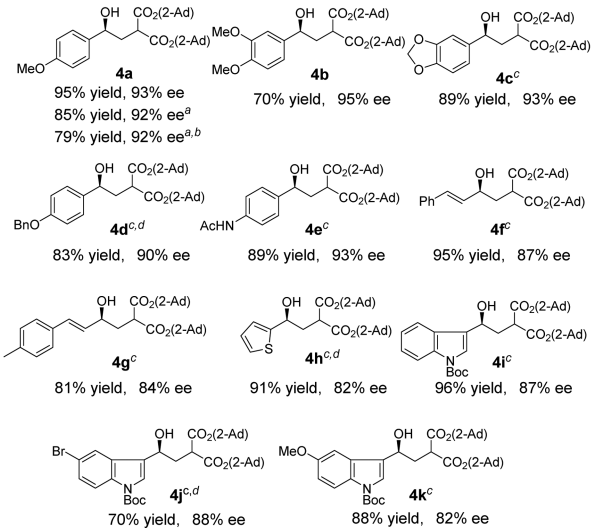
91% yield, 66 ^{18}O%

To examine the generality of this strategy, we studied the scope of the enantioselective ring-opening reaction (Table 4). D−A cyclopropanes with substituents containing various alkoxy and acyl amino groups on the phenyl ring all reacted smoothly with excellent enantioselectivity (70−95% yields, 90−95% ee, **4a**−**4e**).[11,12] The current catalyst system can also be applied to substrates bearing cinnamyl and substituted cinnamyl groups, providing the corresponding products **4f**−**4g** in good to high yields with high levels of enantioselectivity. Notably, these classes of products would be generally difficult to prepare by traditional carbonyl reduction methods due to the sensitive carbon−carbon double bonds. Furthermore, heterocyclic substrate such as 2-(2-thienyl) cyclopropane 1,1-diesters was well tolerated (**4h**). Notably, 3-indolyl substituted cyclopropanes with both electron-donating and -withdrawing groups could result in 70−96% yields

Table 4. Substrate Scope.[a]



91% yield, 66 ^{18}O%



Under Ar atmosphere at rt, **1** (0.20 mmol) $Cu(ClO_4)_2{\cdot}6H_2O$ (0.030 mmol), **L8** (0.036 mmol) in DME (2.0 mL), isolated yield based on **1**. [a]2.0 mmol of **1a** was used. [b]5 mol % of **L8**/$Cu(ClO_4)_2{\cdot}6H_2O$. [c]$[\mathbf{1}]_0$ = 0.20 M in DME (1.0 mL). [d]At 40 °C.

with 82−88% ee (**4i**−**4k**). Notably, the current reaction is easily scaled up. As shown in Table 4, 85% yield was obtained with 92% ee when 2 mmol of **1a** was employed. Lowering the catalyst loading to 5 mol % on gram-scale reaction, 79% yield of **4a** (830 mg) was afforded without loss of the enantiopurity.[12]

In conclusion, we have developed a new strategy where the hydrate copper serves as both a Lewis acid and a source of nucleophile in the first H_2O-nucleophilic enantioselective ring-opening reaction of D−A cyclopropanes. With the **L8**/Cu(II) as catalyst, the reaction performed very well over a broad range of substrates, leading to the ring-opening products in 70−96% yields with up to 96% ee under mild conditions. This method provides a new approach to directly access γ-substituted GBH derivatives very efficiently from activated cyclopropanes. Importantly, the strategy by employing a hydrate catalyst as a reservoir to controlled-release of water might pave a way for asymmetric H_2O-nucleophilic reactions. Further study on the applications of this methodology is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10310.

Experimental procedures, characterizations and analytical data of products, and spectra of NMR and HPLC (PDF)

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Notes

The authors declare no competing financial interest.

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