

Communication

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Asymmetric H₂O-Nucleophilic Ring-opening of D-A Cyclopropanes: Catalyst Serves as a Source of Water

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Supporting Information Placeholder

ABSTRACT: The first catalytic enantioselective ring-opening reaction of D-A 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(ClO₄)₂·6H₂O proves to serve as both a Lewis acid and a source of water, which affords a fine system to controllable release water as a nucleophile in the asymmetric catalysis.

Owing to their flexible reaction patterns and versatile approaches for further elaboration of the products, donoracceptor (D-A) cyclopropanes are considered as useful synthetic building blocks and have attracted increasing attention of synthetic chemists in recent years.¹ Asymmetric ringopening annulations² 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 appeared,²⁻⁴ however, no successful examples on their asymmetric versions are described except that the enantioselective ring-opening reactions of D-A cyclopropanes with secondary amines and indoles.⁵ As our ongoing research on the asymmetric ring-opening of D-A cyclopropanes, we are interested in developing asymmetric reaction of H₂O⁶ with D-A cyclopropanes, a potential approach to optically active GHB acid derivatives.⁷ In the past several years, it proves very challenging since water is a weak nucleophile and the corresponding product alcohol is more nucleophilic than water, which leads to competing by-products 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 In this communication, we wish to 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 ring-opening reaction, we chose alcohol as a model substrate instead of water for the initial study. We first employed In-TOX/Ni(ClO₄)₂ as the catalyst, which is optimal in the reaction of amine with D–A

cyclopropane 1a, and tested 5.0 equivalents 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 in DME. Thus, we turned catalyst system other and found that to Cu(OTf)₂/bisoxazoline (BOX) could promote this reaction (Table 1). After optimizing the solvents, Lewis acids, 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 sidearm (SA) on the bridge carbon of BOX also influenced the results.

Table 1. Optimization of Reaction Conditions.^a

PMP	CO ₂ (2-Ad) CO ₂ (2-Ad) 10 mol% OB 1a L/Cu(OTf) ₂ + PhF, 40 °C PMP 2a	n CO ₂ (2-Ar CO ₂ (2 3a	d) L=Ad)	SA O
entry	SA/L	T(°C)	yield(%) ^b	ee (%) ^c
1	H/L1	40	87	80
2	Ph/L2	40	81	84
3	$3,5^{-t}Bu_2C_6H_3/L_3$	40	65	82
4	3,5-(OCH ₃) ₂ C ₆ H ₃ /L4	40	82	86
5	3,4,5-(OCH ₃) ₃ C ₆ H ₃ /L5	40	74	81
6	/L6	40	82	87
7	/L7	40	89	85
8		40	88	89
9		0	87	93
10 ^d		0	90	93

^{*a*} Conditions: All reactions were carried out under Ar atmosphere, **1a** (0.44 mmol), **2a** (0.20 mmol), $Cu(OTf)_2$ (0.020 mmol), L (0.024 mmol) in C₆H₅F (2.0 mL) and 4 Å MS (200

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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).

As shown in Table 1, 84% ee could be obtained by installing phenyl as a side arm (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 was 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 electron 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 synthetic 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 ring-opening reaction also worked well with 1-octanol 2d, giving the target products 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

	CO ₂ (2-Ad) →CO ₂ (2-Ad) + R ²	OH 10 mol% L8/ Cu(C		O ₂ (2-Ad)
R ¹	1	fluorobenzene 4Å MS, 0 °C	R' 🎺 3	`CO ₂ (2-Ad)
entr	y R ¹	$R^{2}(2)$	3 /yield(%) ^b	ee(%) ^c
1	4-MeOC ₆ H ₄	Bn (2 a)	3a /90	93
2^{d}	$4-BrC_6H_4$	Bn (2 a)	3b /89	96
3	2-thienyl	Bn (2 a)	3 c /92	90
4	4-MeOC ₆ H ₄	cinnamyl (2b)	3d /92	94
5	4-MeOC ₆ H ₄	propargyl (2c)	3e /70	93
6	4-MeOC ₆ H ₄	n-octyl (2 d)	3f /79	94
7	4-MeOC ₆ H ₄	TBSOCH ₂ CH ₂ (2e)	3g / ₇₃	93
8	4-MeOC ₆ H ₄	ⁱ Pr (2f)	3h /80	94

^{*a*} Conditions: All reactions were carried out under Ar atmosphere at o $^{\circ}$ C, 1 (0.44 mmol), 2 (0.20 mmol), Cu(OTf)₂ (0.020 mmol), L8 (0.024 mmol) in C₆H₅F (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. Based on the former scrupulous evaluation, we employed Cu(OTf)₂/Cy-TOX as the catalyst and treated racemic D–A cyclopropane **1a** with 5.0 equivalents 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).

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 (eq.2). In this case, the D-A cyclopropane 1a was all consumed and a product-initiated nucleophilic ring opening by-product 5 was isolated as a main by-product. 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 additional 5.0 equivalents of water. Only 23% yield was obtained with a big surplus of cyclopropane, and no by-product 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 addition of 4Å 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 and the undesired alcohol nucleophilic ring opening reaction. Further screening carefully on the water loading (Figure 1, for 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 remained 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 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(ClO₄)₂·6H₂O could lead to 57% yield (entry 6), 15 mol% of the Cu(ClO₄)₂·6H₂O 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).

Table 3. Optimization of Reaction Conditions.^a

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PMP	CO ₂ (2-Ad) /	mol% L8 /Cu(vent, 40 °C		CO ₂ (2-Ad) CO ₂ (2-A	Ad)
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 ·6H ₂ O	DME	0	71	89
6^d	Cu(ClO ₄) ₂ ·6H ₂ O	DME	0	57	90
7^e	Cu(ClO ₄) ₂ ·6H ₂ O	DME	0	92	90
8 ^{e,f}	Cu(ClO ₄) ₂ ·6H ₂ O	DME	0	95	93
9^g	$Cu(ClO_4)_2 \cdot 6H_2O$	DME	0	0	-

^{*a*} Conditions: All reactions were carried out 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 loading. ^{*e*} With 15 mol% catalyst loading, in 2.0 mL of DME. ^{*f*} At room temperature. ^{*g*} 4 Å MS (200 mg).

Scheme 1. Effects of the Water Loading.



Figure 1. Relationship of the 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), $[1a]_0 = 0.20$ M in DME (1.0 mL), Isolated yield based on 1a.

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 ¹⁸O% of the **4a**-¹⁸O 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.



To examine the generality of this strategy, we studied the scope of the enantioselective ring opening reacion (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 electron-withdrawing groups could resulted in 70-96% yields 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. Lowing the catalyst loading to 5 mol% on gram-scale reaction, 79% yield of the desired product (830 mg) was afforded without loss of the enantiopurity. 12

In conclusion, we have developed a new strategy that the hydrate copper serves as both a Lewis acid and a source of nucleophile in the first H₂O-nucleophilic enantioselective ring-opening reaction of D-A cyclopropanes. With the Cy-TOX/Cu(II) as catalyst, the reaction performed very well over a broad range of substrates, leading to the ring opening products in excellent yields (up to 96%) with excellent levels of enantioselectivity (up to 96% ee) under mild conditions. This method provides a new approach to access directly to γ -substituted GBH derivatives very efficiently from activated cyclopropanes. Importantly, the strategy by employing hydrate catalyst as a reservoir to controlled-release of water might pave a way for asymmetric H₂O-nucleophilic reactions. Further study on the applications of this methodology is underway.

Table 4. Substrate Scope.^a





Conditions: All reactions were carried out under Ar atmosphere at rt, 1 (0.20 mmol) Cu(ClO₄)₂·6H₂O (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(ClO₄)₂·6H₂O. ^{*c*}[1]₀ = 0.20 M in DME (1.0 mL). ^{*d*} At 40 °C.

ASSOCIATED CONTENT

Experimental procedures, characterizations and analytical data of products, and spectra of NMR and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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