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The New Catalyst System: Chloramphenicol Base and Organic Acid Co-catalyzed Enantioselective Alcoholysis of *meso*-Anhydride

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ABSTRACT In this study, the synergistic catalytic strategy was developed, which chloramphenicol base and organic acid were used in the same system, the optimal enantioselectivity value and yield (96% yield; 65% ee) was achieved using the binary co-catalyst in the asymmetric alcoholysis reaction of *meso*-anhydride. Moreover, a hypothetical intermediate between the substrate and the binary co-catalyst which is responsible for stereochemistry control in this catalytic reaction was proposed. In addition, the results of molecular mechanics calculations also have shed light on the corresponding catalytic mechanism.

KEYWORDS Asymmetric alcoholysis, Cyclic anhydride, Co-catalysis, Stereochemistry control, Molecular mechanics

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INTRODUCTION

Over the past decade, the asymmetric alcoholysis of *meso*-anhydrides promoted by organocatalysts is one of the most convenient methods to access optically active hemiesters with either single or multiple stereocenters.[1] These important chiral hemiesters can easily be transformed into other valuable chiral building blocks for the total syntheses of numerous natural products or biologically active substances, including pregabalin,[2] GABOB,[3,4] and (+)-biotin.[5,6]

The unimolecular *Lewis* base catalyst was a proven strategy to achieve a highly enantioselective organocatalytic desymmetrization of *meso*-anhydrides in recent years.[7,8] However, the disadvantages resulting from the self-aggregation of *Lewis* base catalysts cannot be ignored.[9] This leads to that the reactivity has a strong dependence on the substrate concentration and low-temperature conditions.[10] In addition, one imperfection is that the synthesis of catalysts sometimes requires a multistep synthesis and column chromatography was often a necessary step.[11] Undoubtedly, these disadvantages limited its application in industrial production. Therefore, it is necessary to develop a novel method for the organocatalytic asymmetric alcoholysis.

More recently, a synergistic catalytic system established by quinine and organic acid, which was applied in organocatalytic asymmetric alcoholysis of *meso*-anhydride has been reported by Ivšić *et al*.[12,13] This method reported ring-opening reaction of anhydride **1** by utilizing 0.1 equiv quinine and xanthene-9-carboxylic acid at room temperature and gave the corresponding benzyl hemiester with up to 73% ee. On the other hand, Chen's group has successfully applied the chloramphenicol base derivative **3a** to the asymmetric total synthesis of (+)-biotin.[14,15] These novel strategies have attracted our attention due to the parallels with our ongoing research concerning the asymmetric alcoholysis reaction of *meso*-anhydride with chloramphenicol base derivative **3a** as *Lewis* base catalyst [**Scheme 1**].

RESULTS AND DISCUSSION

Encouraged by the promising result reported by Ivšić *et al*.,[12,13] we extended our methodology towards the

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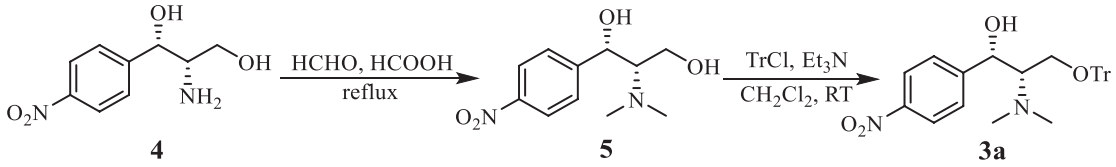


4 5 3a

Scheme 1: General procedure for preparation of target catalyst 3a

above mentioned binary co-catalyst system. As a first step, therefore, we performed this reaction under similar condition to check the potential of **3a** and xanthene-9-carboxylic acid as the binary co-catalyst. The binary co-catalyst was assessed in catalytic stereoselective opening of anhydride **1** using MeOH as nucleophile at room temperature. The binary co-catalyst gave smooth desymmetrization to hemiester **2** in 30% enantioselectivity value (**Table 1**, entry 1). The results which presented in **Table 1** indicated that the benefit of improving the enantioselectivity with xanthene-9-carboxylic acid as additive (**Table 1**, entry 2 and entry 6).

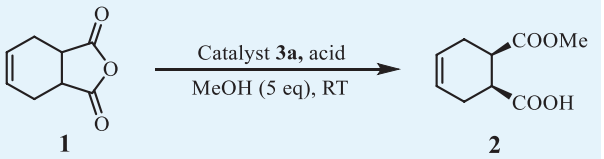
In light of the above positive results, the effect of catalyst loading was investigated on the reaction. These results point toward the optimal catalyst loading was 0.3 equivalent. To our surprise, the enantioselectivity value of the asymmetric alcoholysis reaction would become worse when the catalyst loading was increased (**Table 1**, entry 3 - entry 5).

With the optimized reaction conditions in hand, we went on to investigate the solvent effect. Obviously, the optimum solvent in terms of enantioselectivity was $CHCl_3$ (**Table 2**, entry 10). It could be reasonably inferred that aprotic solvents performed better than protic solvents from these results which presented in **Table 2**. Furthermore, optimization of the reaction concentration revealed that 0.05 M was the optimal condition for this reaction (**Table 2**, entry 10–14).

For acid additives, the enantioselectivity of the reaction reached its optimum value at a base/acid ratio of 1:2 (**Table 3**, entry 2). In addition to that, the influence of various acids as additives was also studied. The results of experiments revealed that the optimal enantioselectivity were achieved with short chain fatty acid (**Table 4**, entry 5 and 6) as well as with xanthene-9-carboxylic acid (**Table 4**, entry 7). Under the optimum conditions, the reactions of anhydride **1** and various alcohols including EtOH, *i*-PrOH, BnOH, propargyl alcohol, *trans*-cinnamyl alcohol were also taken consideration. We have founded that if methanol was replaced by aromatic alcohols, the enantioselectivity values were increased (**Table 4**, entries 10 and 12). Moreover, an inversion of enantioselectivity in the asymmetric alcoholysis of anhydride **1** with allyl alcohol was observed (**Table 4**, entry 11).

The methanolysis of *meso*-anhydride **1** has been submitted to a computational study to provide a theoretical explanation for the principal configuration of the hemiester **2**. The calculation was carried out by Gaussian 03 program package.[16] Geometry optimization was performed using density functional theory (B3LYP-D3/6–31 g (d, p)). Optimal conformation composed of catalyst **3a**, methanol and anhydride (**1**) can be obtained using the empirical, dispersion corrected B3LYP-D3 method with the 6–31 G(d,p) basis set.

Table 1: Influence of catalyst loading on the desymmetrization of anhydride (1) with MeOH[a]

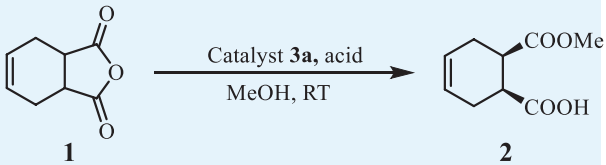


1 2

Entry	Equiv	Acid (X9C)	Time/h	Yield/%	Ee[c]/%
1	0.1	0.2	24	89	30
2	0.3	0.6	4	96	54
3	0.5	1.0	12	90	38
4	0.7	1.4	4	69	32
5	1.1	2.2	4	94	3
6	0.3	none	6	97	30[b]

[a]Reaction conditions: 0.1 M anhydride **1** in chloroform solution, 0.2–2.2 equiv of xanthene-9-carboxylic acid (X9C), 5 equiv of MeOH, rt. [b]Reaction without acid as additive. [c]Determined by chiral HPLC on Chiralcel OD-H (*n*-hexane/isopropanol=93:7)

Table 2: Influence of the solvent and concentration on the methanolysis of *meso*- cyclic anhydride (1)[a]



1 2

Entry	Solvent	Time/h	Yield/%	Conc./M	Ee[b]/%
1	DCM	6	95	0.1	31
2	EtOAc	6	95	0.1	35
3	Et_2O	12	97	0.1	41
4	Acetone	4	93	0.1	31
5	THF	12	91	0.1	43
6	Dioxane	12	90	0.1	52
7	CCl_4	10	98	0.1	43
8	Toluene	4	93	0.1	53
9	MTBE	12	87	0.1	30
10	$CHCl_3$	4	96	0.1	54
11	$CHCl_3$	2	97	0.2	47
12	$CHCl_3$	6	94	0.05	57
13	$CHCl_3$	12	90	0.025	53
14	$CHCl_3$	24	91	0.0125	44

[a]Reaction conditions: 0.2–0.125 M anhydride **1** solution, 0.3 equiv of organocatalyst **3a**, 0.6 equiv of xanthene-9-carboxylic acid (X9C), 5 equiv of MeOH, rt. [b]Determined by chiral HPLC on Chiralcel OD-H (*n*-hexane/isopropanol=93:7)

The complexes **TS** and **TS'** could be regarded as transition-state analogues of the noncatalytic *meso*-anhydride **1** methanolysis reaction [**Figure 1**]. The complex

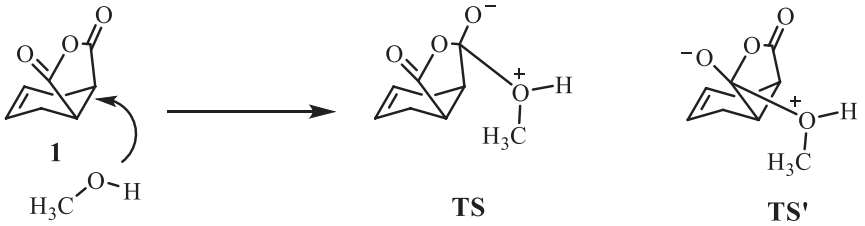
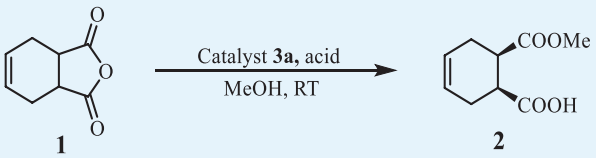


Figure 1: Transition state analogues of uncatalyzed methanolysis of anhydride 1

Table 3: Catalyst/acid ratio effect on methanolysis the of *meso*-cyclic anhydride (1)[a]



Entry	Catalyst	Acid (X9C)	Time/h	Nu	Yelid	Ee[b]/%
1	0.3	0.3	2	MeOH	87	41
2	0.3	0.6	6	MeOH	94	57
3	0.3	0.9	4	MeOH	93	50
4	0.3	1.2	6	MeOH	91	41
5	0.3	1.5	12	MeOH	90	39

[a]Reaction conditions: 0.05 M anhydride **1** chloroform solution, 0.3 equiv of catalyst **3a**, 0.3–1.5 equiv of xanthene-9-carboxylic acid (X9C), 5 equiv of MeOH, rt. [b]Determined by chiral HPLC on Chiralcel OD-H (*n*-hexane/isopropanol=93:7)

(**3a-TS** complex) was stabilized through the interaction of two complementary hydrogen bonds according to speculate. These complexes can be approximated as transition state analogues of the reaction path [**Figure 2**]. The result [**Figure 2A**] we compute indicated that two hydrogen bonding interactions have played an important role on the stabilization of complex, which consist of catalyst **3a**, methanol and anhydride (**1**): (i) between the protonated tertiary amine group and the methanol hydroxyl proton; (ii) between the catalyst hydroxyl hydrogen and an oxyanion attached to the carbonyl carbon of the anhydride.

While acetic acid was used as additive, the lowest conformation of the acetic acid, catalyst **3a**, methanol, and anhydride (**1**) complex was explored at the B3LYP-D3/6-31G(d) level of theory. Surprisingly, we found that the acetic acid has replaced methanol in the hydrogen bond with the tertiary amine [**Figure 2B**]. The new complex **3a-TS-acid** were stabilized by three hydrogen bond interaction which composed of (i) between the catalyst protonated tertiary amine group and the acetic acid, (ii) between the acetic acid hydroxyl and methanol hydroxyl proton and (iii) between the catalyst hydroxyl hydrogen and an oxyanion attached to the carbonyl carbon of the anhydride. It is apparent**,** the new complex **3a-TS-acid,** which benefited from better hydrogen bond interaction, would be more stable in contrast with the complex **3a-TS.** Moreover, the calculations also have shown that the new complex **3a-TS-acid** is 2.9 kcal·mol^{-1} more stable than the complex **3a-TS.** This is consistent with the hydrogen bonding interaction we observed in **Figure 3**. These energy differences also explain the reason of the higher selectivity of catalyst system while the acid as additive.

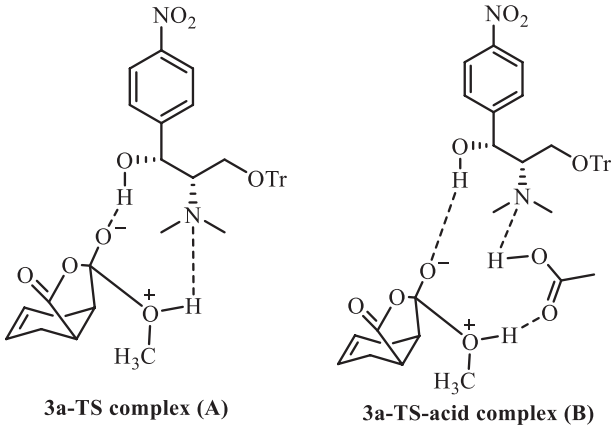


Figure 2: Transition state analogues of catalyzed process

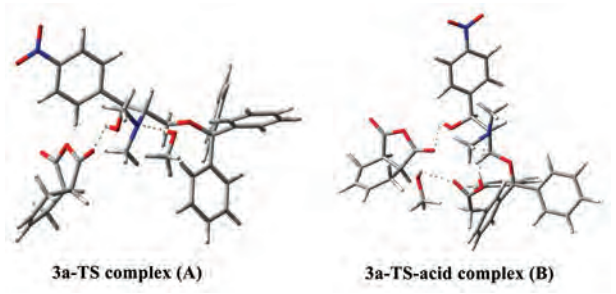


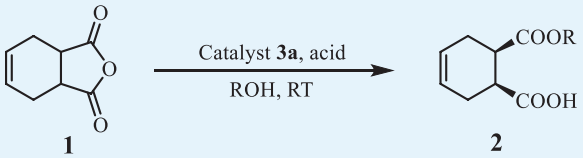
Figure 3: The structures of the lowest energy conformer 3a-TS complex and 3a-TS-acid complex

In conclusion, a novel catalytic system based on chloramphenicol base-acid complex was investigated in detail. All intermediate products in the optimal catalyst **3a** synthesis path were allowed to be obtained without column chromatography. The study of acid additives revealed that enantioselectivity can be increased to 65%—a level which might be of synthetic interest. Furthermore, molecular mechanics calculations were performed to provide the theoretical explanation for the higher selectivity while the acid as additives. The results may also contribute to detailed insight into the mechanism of the chloramphenicol base-acid catalyzed methanolysis of *meso*-anhydrides.

EXPERIMENTAL SECTION

All the solvents were purified by distillation prior to use. Unless otherwise specified, all other chemicals used in this study were purchased from Adamas-Beta and used without further purification. Melting points were measured on WRS-1B digital melting-point apparatus. Products were purified by flash column chromatography on silica gel purchased from

Table 4: Influence of acid additives and various alcohols on methanolysis the of *meso*-cyclic anhydride (1)[a]



1 2

Entry	Acid	Nu	Product	Time/h	Yield/%	Ee[b]/%
1	Aluminium chloride	MeOH	**2a**	24	89	4
2	*L*-(+)-tartaric acid	MeOH	**2a**	12	93	44
3	*DL*-Mandelic acid	MeOH	**2a**	12	90	37
4	HCOOH	MeOH	**2a**	4	69	-
5	CH_3COOH	MeOH	**2a**	4	94	52
6	CH_3CH_2COOH	MeOH	**2a**	4	97	53
7	X9C	MeOH	**2a**	6	94	57
8	X9C	EtOH	**2b**	4	95	14
9	X9C	i-PrOH	**2c**	120	n.r.	n.r.[c]
10	X9C	allyl alcohol	**2d**	4	93	55
11	X9C	BnOH	**2e**	6	91	−30
12	X9C	cinnamyl alcohol	**2f**	4	96	65

[a]Reaction conditions: 0.05 M anhydride **1** chloroform solution, 0.3 equiv of catalyst **3a**, 0.6 equiv of acid, 5 equiv of ROH, rt. [b]Determined by chiral HPLC on Chiralcel AD-H (n-hexane/isopropanol = 90:10, entries 11 and 12) or Chiralcel OD-H (*n*-hexane/isopropanol=93:7, entries 1–10). [c]Not reacted completely after 120 h

Qingdao Haiyang Chemical Co. Ltd. Optical rotations were measured by a Rudolph AUTOPOL I Automatic Polarimeter. HPLC analysis was performed using Daicel AD-H column (0.46 cm × 25 cm × 5 μm) or Chiralcel OD-H column (0.46 cm × 25 cm × 5 μm). ^1H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet.

General procedure for the asymmetric alcoholysis of *meso*-anhydride

To a solution of catalyst **3a** and organic acid in chloroform ($CHCl_3$) was added *meso*-anhydride at room temperature under nitrogen. After being stirred for 10 min, alcohol was added dropwise. After the completion of addition, the resulting mixture was stirred at the room temperature for 24 h. Subsequently, the organic phase was concentrated under vacuum to give the crude product. The residue was dissolved in dichloromethane, washed with 1 M Na_2CO_3 (30 mL × 2). The combined aqueous phase was acidified with excess 1 M HCl, followed by extraction with dichloromethane (20 mL × 3). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated to afford the corresponding hemiester.

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