Communication

Chiral Phosphoric Acid-Catalyzed Kinetic Resolution via Amide-Bond Formation

Yasushi Shimoda, and Hisashi Yamamoto

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Chiral Phosphoric Acid-Catalyzed Kinetic Resolution *via* Amide-Bond Formation

Yasushi Shimoda* and Hisashi Yamamoto*

Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto-cho, Kasugai, Aichi, 487-8501, Japan

Supporting Information Placeholder

ABSTRACT: We describe a kinetic resolution of readily available 2-pyridyl ester *via* an amide-bond formation catalyzed by a chiral Brønsted acid. A chiral phosphoric acid bearing 2,4,6-trimethyl-3,5-dinitrophenyl group at 3,3'-position enabled this transformation with high selectivities. Additionally, We also found that the addition of Lewis acid increased both the reactivity and selectivity in the substrate with methoxy group.

Optically active carboxylic acid derivatives are highly important and fundamental motifs found in a wide variety of natural products, biologically active and pharmaceutically useful compounds (Figure 1).[1] As a consequence, the preparation of chiral carboxylic acid derivatives has received much attention in organic chemistry. Although asymmetric hydrogenation of α,β-unsaturated carboxylic acids[2] or asymmetric alkylation of achiral carboxylic acids[3] is known to be the direct method for the preparation of such chiral carboxylic acids with an α-stereogenic center, they sometimes require the complicated preparation of starting materials or catalysts.

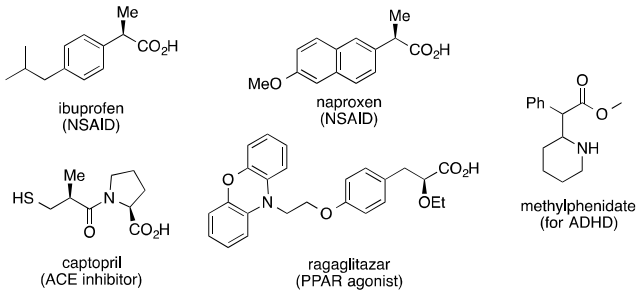


Figure 1. Examples of pharmaceutical compounds bearing carboxylic acid or its derivatives with α-stereogenic center

On the other hand, separation of racemic chiral carboxylic acids can be a straightforward route to afford the optically pure carboxylic acids. It has been well studied that the enzymes are generally used for the kinetic resolution (KR) of racemic substrates, affording enantiomerically pure compounds.[4] It is also well established that racemic carboxylic acids can be separated into a diastereomeric salt by recrystallization in the presence of a stoichiometric or excess amount of a chiral amine. However, these methods are not always useful and require an excess amount of reagents, leading to poor atom economy. In contrast, catalytic KR reactions allow the separation of racemic compounds without use of stoichiometric amount of reagents. Although various catalytic KR methods of amines via an amide bond formation[5] or other transformations[6] have been developed, the catalytic KR of carboxylic acid or its derivatives is still a challenging research subject. Pioneering works on catalytic KR of carboxylic acids using esterification have been developed by Ishihara[7] and Shiina[8]. Their methods show high selectivities with various substrate scopes but requires pre-activation of carboxylic acids.

We present herein a new strategy for the kinetic resolution of carboxylic acid derivatives catalyzed by chiral phosphoric acid. We envisioned that esters bearing pyridine moiety could interact with a proton from chiral Brønsted acid to form a chiral ion pair,[9] which enables kinetic resolution of racemic esters through an amide-bond formation reaction[10] with an amine as a nucleophile (Figure 2). It is known that pyridyl esters can be used as an active ester[11] for amide bond formation reactions,[12] however, to the best of our knowledge, there are no examples of its application to asymmetric synthesis.

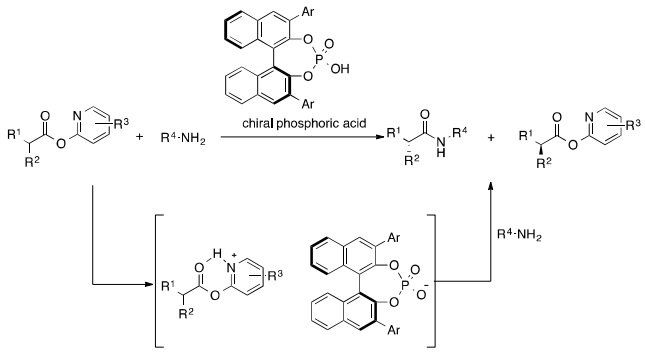
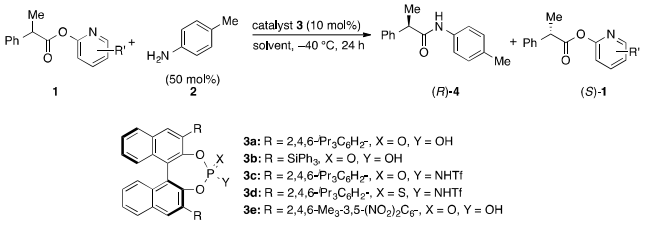


Figure 2. Working hypothesis of KR reaction

We commenced our studies on the KR reaction of 2-pyridyl ester **1** with *p*-toluidine (**2**) as a nucleophile in toluene using a chiral phosphoric acid **3a** (Table 1, entry 1). With non-substituted pyridyl ester, the reaction proceeded smoothly but only a low *s* factor was detected (entry 1). To improve the selectivity, we introduced a methyl group onto the pyridine ring and found that substituent on the 6-position increased the selectivity (entry 3). The reaction did not proceed in the substrate with phenyl group at the 6-position probably due to its steric hindrance (entry 4). Subsequently, various phosphoric acid catalysts (entries 3, 5-8) were evaluated. Among the catalysts tested, the phosphoric acid bearing 2,4,6-trimethyl-3,5-dinitrophenyl group at 3,3'-position, which was developed by our group,[13] was found to be efficient catalyst for this KR reaction (entry 8, *s* factor = 20). Stronger Brønsted acids, such as phosphoramide **3c** or thiophosphoramide **3d**, gave almost racemic products because of its high acidity (entries 6 and 7). Other solvents did not improve the reactivity and selectivity (entries 9 and 10). The catalyst loading could be reduced to 5 mol% without loss of reactivity and selectivity (entry 11).

Table 1. Screening of reaction conditions[a)]

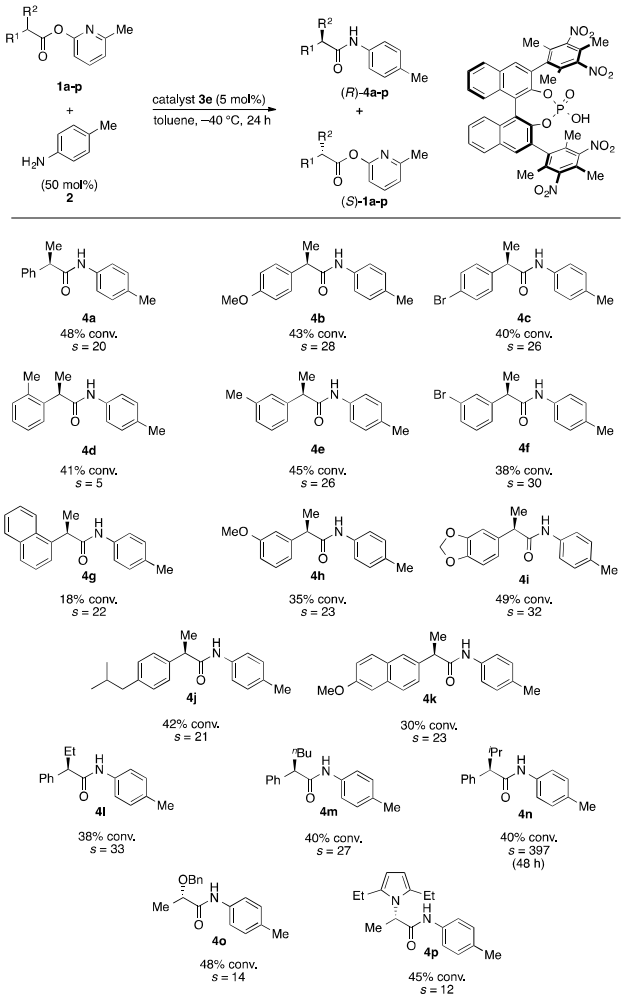


entry	R'	catalyst	solvent	conv. (%)	*s*
1	H	**3a**	toluene	30	3
2	3-Me	**3a**	toluene	39	2
3	6-Me	**3a**	toluene	30	12
4	6-Ph	**3a**	toluene	NR	-
5	6-Me	**3b**	toluene	30	2
6	6-Me	**3c**	toluene	26	0
7	6-Me	**3d**	toluene	24	0
8	6-Me	**3e**	toluene	48	20
9	6-Me	**3e**	Et_2O	12	1
10	6-Me	**3e**	CH_2Cl_2	10	0
11[b)]	6-Me	**3e**	toluene	47	20

a) ee, conv., and *s* factor were determined by ^{1}H NMR and HPLC. b) Reaction was performed with 5 mol% of catalyst.

With the optimal conditions in hand, we applied this KR reaction to a wide variety of substrates (Scheme 1). Although the substituent at the 2-position on the benzene ring decreased the selectivity, various substrates showed the similar reactivities and selectivities (**4a**-**4k**). Substitution at the 3-position increased the selectivities. The carboxylic acid analogues of **1j** and **1k** are well known to be medicinal drugs (Figure 1). These substrates also could be separated by our KR method to afford corresponding amide products **4j** and **4k** with good *s* factors. Notably, substitution of the methyl group to the bulkier alkyl group (**4l**-**4n**) showed the influence to the selectivity. An extremely high *s* factor (*s* = 397) was observed with compound bearing isopropyl group **4n**. This KR method also separated the heteroatom-containing carboxylic acid derivatives at the α-position. After preliminary screening of the protecting group, both oxygen and nitrogen-containing substrate showed good *s* factor (**4o** and **4p**).

Scheme 1. Examples of substrates in the KR reaction[a)]

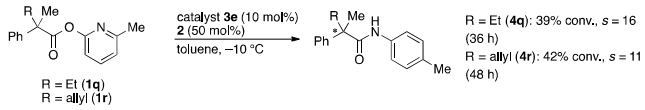


a) ee, conv., and *s* factor were determined by ^{1}H NMR and HPLC.

Additionally, this KR reaction is also successful when we use esters with quaternary stereogenic center, which is difficult to have optical active one using such as hydrogenation methods. The corresponding products were

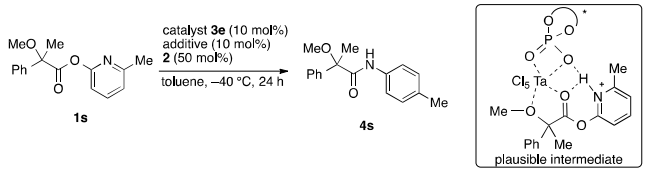
obtained with good selectivities under slightly modified conditions (Scheme 2).

Scheme 2. A kinetic resolution of substrates with quaternary stereogenic center



Interestingly, we found that the addition of Lewis acid[13] improved both the reactivity and selectivity in the substrate bearing methoxy group (Table 2). Although only the low conversion and *s* factor are observed without Lewis acid additive, the use of Lewis acid improved both the reactivity and selectivity. Among the Lewis acids tested[15], tantalum (V) chloride[16] showed efficient catalytic activity to furnish the amide product **4s** with high selectivity (s = 30). We assumed that Lewis acid coordinates to the oxygen atom of the methoxy group to activate the carbonyl group.

Table 2. Additive effect of Lewis acids[a)]

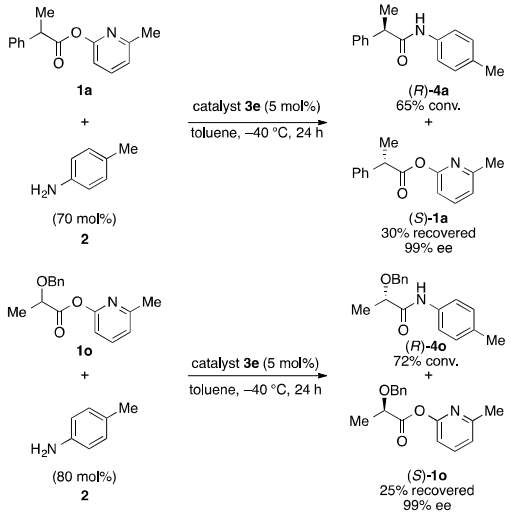


entry	additive	conv. (%)	*s*
1	none	19	3
2	$Mg(OTf)_2$	34	13
3	$NiBr_2$	47	11
4	$La(OTf)_3$	33	11
5	$Hf(OTf)_4$	31	14
6	$NbCl_5$	22	8
7	$TaCl_5$	48	30

a) ee, conv., and *s* factor were determined by ^{1}H NMR and HPLC.

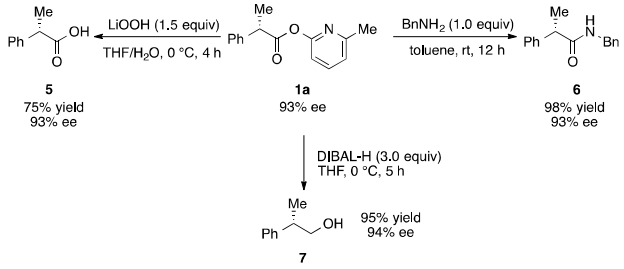
Enantiomerically pure esters could be obtained by using the KR method with a slightly excess amount of amines (Scheme 3). The reaction of **1a** with 70 mol% of **2** affords an amide product with 65% conversion. Gratifyingly, 99% ee was observed in recovered starting material. Similarly, almost optically pure α-hydroxy ester derivative **1o** could be obtained.

Scheme 3. Reaction for the enantiomerically pure esters



The hydroxy pyridyl group in the ester compound **1a** could be removed easily to afford carboxylic acid **5** without loss of enantioselectivity (Scheme 4). More importantly, pyridyl esters are known to be activated carbonyl compounds. Benzylamine reacted smoothly to afford amide compound **6** in high chemical yield. After treatment with DIBAL-H, the corresponding alcohol **7** was obtained in a high chemical yield.

Scheme 4. Derivatization of pyridyl ester



In conclusion, we have developed an enantioselective catalytic KR reaction of pyridyl esters using a chiral Brønsted acid catalyst bearing the 2,4,6-trimethyl-3,5-dinitrophenyl group. This KR protocol shows broad substrate scopes including heteroatom-containing substrate or substrates with quaternary stereogenic center. In addition, the hydroxy pyridyl group can be converted to other derivatives in a simple way. Further studies including the investing of mechanistic studies and application to other transformation are in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Corresponding Author

yshimoda@isc.chubu.ac.jp
hyamamoto@isc.chubu.ac.jp

Notes

No competing financial interests have been declared.

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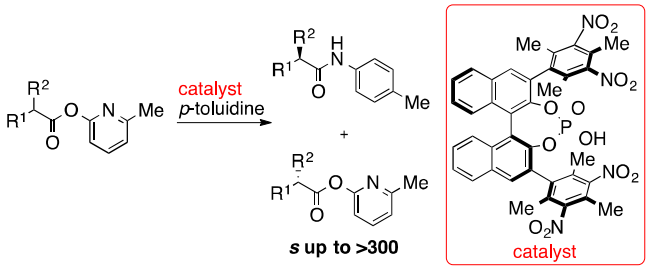
catalyst
p-toluidine
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