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Chiral Phosphoric Acid-Catalyzed Kinetic Resolution of 2-Amido Benzyl Alcohols: Asymmetric Synthesis of 4*H*-3,1-Benzoxazines

Subramani Rajkumar,[a],‡ Mengyao Tang[a],[b],‡ and Xiaoyu Yang[a]*

Abstract: An efficient method for asymmetric synthesis of 4*H*-3,1-benzoxazines was developed via kinetic resolution of 2-amido benzyl alcohols through chiral phosphoric acid catalyzed intramolecular cyclizations. A broad range of benzyl alcohols (both secondary and tertiary alcohols) could be kinetically resolved with high selectivities, with s factor up to 94. Mechanistic studies were performed to elucidate the mechanism of these reactions, in which the amide moieties reacted as the electrophiles. Gram-scale reaction and facile transformations of the chiral products well demonstrate the potential of this method in asymmetric synthesis of biologically active chiral heterocycles.

4*H*-3,1-Benzoxazines, a type of *N,O*-containing six membered heterocycles, are prevalent in a variety of biologically active molecules, such as pharmaceuticals and agrochemicals[1]. For example, etifoxine, a 2-amino-4*H*-3,1-benzoxazine analogue, is a well-known GABA receptor inhibitor and widely used as anxiolytic and anticonvulsant drug[2]. Efavirenz, which featured a 4*H*-3,1-bezoxazin-2-one structure, is a non-nucleoside reverse transcriptase inhibitor that shows high potency against a variety of HIV-1 mutant strains[3] (Figure 1, a). However, despite the fact that a large number of 4*H*-3,1-benzoxazine derivatives possess promising biological activities, methods for their enantioselective synthesis are quite limited. To the best of our knowledge, only two examples of catalytic asymmetric synthesis of 4*H*-3,1-benzoxazines have been reported to date[4]. Toste and co-workers developed asymmetric synthesis of halogenated 4*H*-3,1-benzoxazines via enantioselective halocyclization of *o*-anilidostyrenes under chiral anion phase-transfer catalysis conditions[5] (Figure 1, b). Feringa and co-workers reported catalytic enantioselective synthesis of 4*H*-3,1-benzoxazines via Ir-catalyzed asymmetric intramolecular allylic amidation, however, in which the scope of the chiral centers were limited to vinyl/H-disubstituted type (Figure 1, c)[6]. Furthermore, in the sense of asymmetric induction strategy, both of these methods could be viewed as utilization of the amide groups as nucleophiles to attack the “chiral electrophiles”. Therefore, development of new strategy for enantioselective synthesis of 4*H*-3,1-benzoxazines, which has broad substrate scopes, are still highly demanding.

Kinetic resolution is one of the most reliable and practical approaches to generate enantioenriched alcohols[7]. However, in contrast to the well-developed methodologies for kinetic resolution of secondary alcohols, highly efficient kinetic resolution for tertiary alcohols (either through enzymatic[8] or nonenzymatic catalysis[9]) was relatively limited. With our continuous interest on highly efficient kinetic resolution of tertiary alcohols,[10] herein we disclose a novel protocol for asymmetric synthesis of 4*H*-3,1-benzoxazines via kinetic resolution of 2-amido benzyl alcohols[11] (both tertiary and secondary alcohols) through chiral phosphoric acids (CPA)[12] catalyzed intramolecular cyclizations[13]. (Figure 1, d).

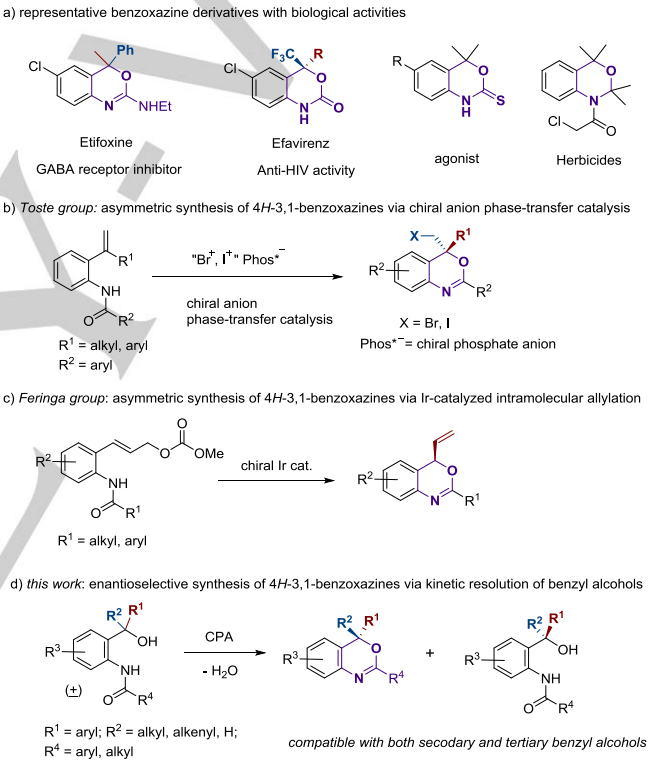

Figure 1. a) biologically active 4*H*-3,1-benzoxazine derivatives; b) asymmetric synthesis of 4*H*-3,1-benzoxazines via halocyclization by Toste group; c) asymmetric synthesis of 4*H*-3,1-benzoxazines via intramolecular allylic amidation by Feringa group; d) this work: asymmetric synthesis of 4*H*-3,1-benzoxazines via kinetic resolution of 2-amido benzyl alcohols.

We initiated our study with the observation that cyclization of 2-amido tertiary benzyl alcohol **1a** produced 4*H*-3,1-benzoxazine **2a** under the catalysis of CPA catalyst[14], which we envisioned may be utilized for kinetic resolution of benzyl alcohols. However, under the catalysis of CPA **A1** (10 mol %), the kinetic resolution of substrate **1a** in toluene in the presence of 5 Å molecular sieves provided poor results at 25 °C, with selectivity factor (s)[15] of 1.4 (Table 1, entry 1). Subsequently, a variety of BINOL-derived CPA catalysts were examined in this reaction (entries 2-8); encouragingly, the 3,3’-triphenylsilyl (TPS) substituted CPA catalyst **A8** provided dramatically improved results, with s factor of 54 (entry 8). Interestingly, switching the silyl group from TPS group to the tert-butyldiphenylsilyl (TBDPS)

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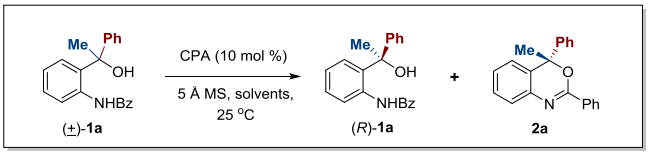
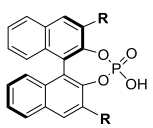
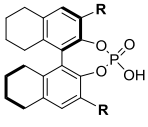
group almost led to the loss of kinetic resolution selectivity (entry 9). Replacing the chiral scaffold of catalyst from BINOL-type into H8-BINOL-type also led to the erosion of s factor (entry 10). A range of solvents were then screened with catalyst **A8** (entries 11-13), which indicated that toluene still as the optimal solvent. The role of 5 Å molecular sieves was also demonstrated; in the absence of them, the s factor was decreased to 43 (entry 14).

Table 1. Optimizations of the reaction conditions.[a]





A1, R = 1-napthyl
A2, R = 2-napthyl
A3, R = 9-anthracenyl
A4, R = 9-phenanthryl
A5, R = 2,4,6-$(Me)_3C_6H_2$
A6, R = 2,4,6-$(iPr)_3C_6H_2$
A7, R = 2,4,6-$(Cy)_3C_6H_2$
A8, R = -$SiPh_3$
A9, R = -$SiPh_2tBu$



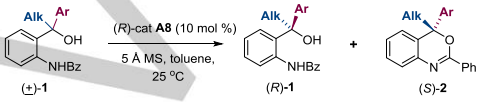
A10, R = -$SiPh_3$

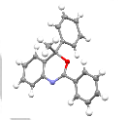
Entry	Cat.	Sol.	er_s[b]	er_p[b]	C[c] (%)	s[d]
1	**A1**	Tol	55:45	56.5:43.5	43	1.4
2	**A2**	Tol	53:47	52.5:47.5	55	1.2
3	**A3**	Tol	68:32	62:38	60	2.2
4	**A4**	Tol	65.5:34.5	72.5:27.5	41	3.5
5	**A5**	Tol	54.5:45.5	67.5:32.5	20	2.3
6	**A6**	Tol	78:22	88.5:11.5	42	13
7	**A7**	Tol	71:29	88:12	36	11
8	***A8***	***Tol***	***95.5:4.5***	***94.5:5.5***	***50***	***54***
9	**A9**	Tol	68.5:31.5	75.5:24.5	42	4.4
10	**A10**	Tol	80:20	93:7	41	24
11	**A8**	CCl_4	97:3	88.5:11.5	55	27
12	**A8**	DCM	70.5:29.5	95.5:4.5	31	32
13	**A8**	$CHCl_3$	72.5:27.5	96.5:3.5	33	43
14[e]	**A8**	Tol	78.5:21.5	96:4	38	43

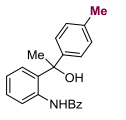
[a]Reactions were run with **1a** (0.1 mmol) with CPA catalyst (0.01 mmol, 10 mol %) in solvent (2 mL) with 5 Å molecular sieves (30 mg) at 25 °C. [b]Determined by HPLC analysis on a chiral stationary phase. [c]Conversion (C) = $ee_s/(ee_s+ee_p)$. [d]s = $\ln[(1-C)(1-ee_p)]/\ln[(1-C)(1+ee_p)]$. [e]Without 5 Å molecular sieves.

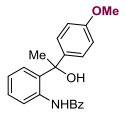
With the optimal conditions in hand, we sought to explore the substrate scope of this reaction. The tertiary alcohol moieties in the substrates were first examined under the optimal conditions (Table 2). A series of aryl/Me-type tertiary benzyl alcohols were exploited, which showed that a range of substituted phenyl groups (with various electron-donating, electron-withdrawing and electron-neutral substitutions at the *para*- and *meta*- positions) could be well tolerated (**1b**-**1h**). The absolute configurations of the recovered benzyl alcohols and products were assigned by analogy to alcohol **1m** and product **2a**, whose structures were unambiguously confirmed by X-ray crystallography[16], indicating that the recovered starting materials and products possessing the opposite stereochemistry. Disubstituted phenyl groups (**1i**-**1j**), 2-naphthyl group (**1k**) and 3-thiophenyl group (**1l**) were also amenable to the optimal conditions. Subsequently, a range of Ph/alkyl-type tertiary benzyl alcohols were exploited with the standard conditions, however, whose kinetic resolution reactions proceeded slowly at 25 °C. Thus, the reaction temperatures were raised to improve the reaction rate; surprisingly, the kinetic resolution of these alcohols at higher temperatures (e.g. 60 °C) still gave excellent performances (with s factor >45). Both primary (**1m**-**1o**) and secondary alkyl (**1p**) groups could be well tolerated, including the allyl (**1q**) and benzyl (**1r**) groups as well. Interestingly, a Ph/vinyl-substituted benzyl alcohol could also be well resolved, albeit with a diminished s factor of 17 (**1s**).

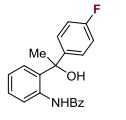
Table 2. Substrate scope regarding to the tertiary alcohol moieties.[a]

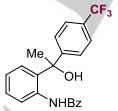


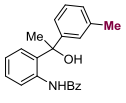

X-ray structure of (*S*)-**2a**

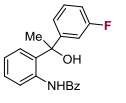

(*R*)-**1b**, 49%, 95.5:4.5 er
(*S*)-**2b**, 49%, 94:6 er
48 h, s = 50

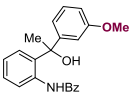

(*R*)-**1c**, 49%, 96.5:3.5 er
(*S*)-**2c**, 48%, 93.5:6.5 er
48 h, s = 49

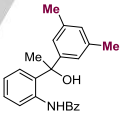

(*R*)-**1d**, 47%, 97:3 er
(*S*)-**2d**, 52%, 92:8 er
36 h, s = 40

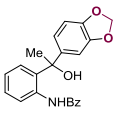

(*R*)-**1e**, 46%, 97:3 er
(*S*)-**2e**, 51%, 88.5:11.5 er
36 h, s = 27

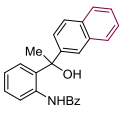

(*R*)-**1f**, 48%, 94.5:5.5 er
(*S*)-**2f**, 49%, 94:6 er
36 h, s = 47

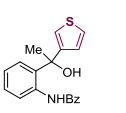

(*R*)-**1g**, 48%, 95.5:4.5 er
(*S*)-**2g**, 47%, 91.5:8.5 er
36 h, s = 32

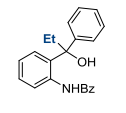

(*R*)-**1h**, 46%, 98:2 er
(*S*)-**2h**, 45%, 96:4 er
64 h, s = 94

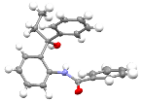

(*R*)-**1i**, 43%, 94.5:5.5 er
(*S*)-**2i**, 49%, 91:9 er
64 h, s = 30

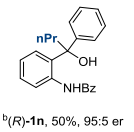

(*R*)-**1j**, 45%, 95:5 er
(*S*)-**2j**, 45%, 93:7 er
48 h, s = 41

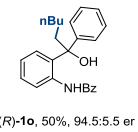

(*R*)-**1k**, 47%, 95:5 er
(*S*)-**2k**, 44%, 93:7 er
60 h, s = 41

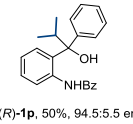

(*R*)-**1l**, 45%, 98:2 er
(*S*)-**2l**, 53%, 88.5:11.5 er
28 h, s = 30

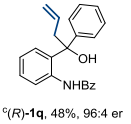

[b](*R*)-**1m**, 49%, 95:5 er
(*S*)-**2m**, 50%, 94:6 er
12 h, s = 48

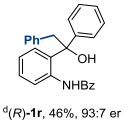

X-ray structure of (*R*)-**1m**

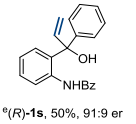

[b](*R*)-**1n**, 50%, 95:5 er
(*S*)-**2n**, 47%, 95:5 er
18 h, s = 58


[b](*R*)-**1o**, 50%, 94.5:5.5 er
(*S*)-**2o**, 48%, 94.5:5.5 er
22 h, s = 51


[b](*R*)-**1p**, 50%, 94.5:5.5 er
(*S*)-**2p**, 47%, 96:4 er
64 h, s = 72


[c](*R*)-**1q**, 48%, 96:4 er
(*S*)-**2q**, 49%, 95.5:4.5 er
64 h, s = 70


[d](*R*)-**1r**, 46%, 93:7 er
(*S*)-**2r**, 43%, 96.5:3.5 er
96 h, s = 77


[e](*R*)-**1s**, 50%, 91:9 er
(*S*)-**2s**, 44%, 87:13 er
48 h, s = 17

[a]Unless otherwise noted, reactions were performed with 0.2 mmol rac-**1**, 0.02 mmol (*R*)-cat **A8** catalyst and 60 mg 5 Å MS in 4 mL toluene at 25 °C. The reactions were monitored by HPLC using a chiral stationary phase. The yields are isolated yields. The er values were determined by HPLC analysis on a chiral stationary phase. [b]At 60 °C. [c]At 40 °C. [d]At 70 °C in $CHCl_3$ (4 mL). [e]At 45 °C.

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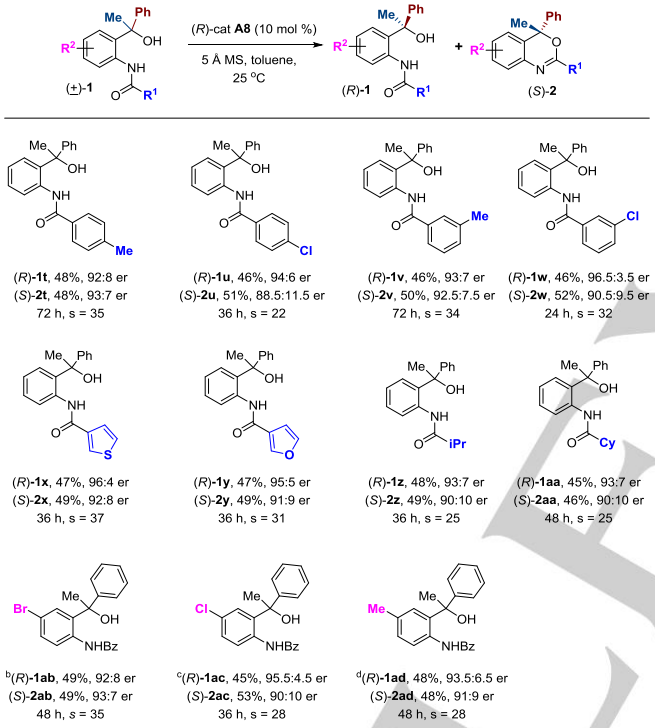
We next explored the substrates bearing various N-acyl substitutions (Table 3). We found that a range of substituted benzoyl groups were well compatible with the optimal conditions (**1t**-**1w**), providing good kinetic resolution performances. Two heteroaryl formyl groups (**1x** and **1y**) were also tolerated, which generated chiral 4*H*-3,1-benzoxazine products bearing heteroaryl substitutions at the 2-position. The alkanoyl groups were also amenable with these conditions, albeit giving products with a bit diminished enantioselectivities (**1z** and **1aa**). Substrates with substitutions at the 5-position of benzyl alcohols were also subjected into investigation, which revealed that a series of substituents at this position were also well compatible with the standard conditions (**1ab**-**1ad**).

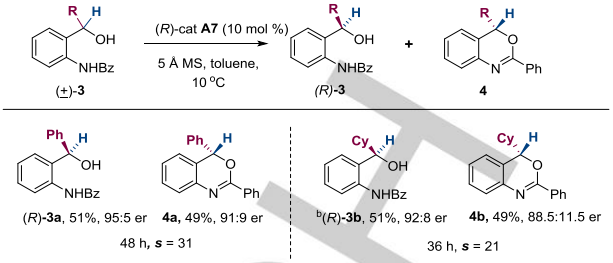
Table 3. Substrate scope regarding to the amide moieties and substitutions on the benzene ring.[a]



[a]Conditions as indicated in Table 2. [b]At 40 °C in $CHCl_3$. [c]At 50 °C in $CHCl_3$. [d]At 30 °C.

To further demonstrate the versatility of this method in asymmetric synthesis of 4*H*-3,1-benzoxazines, kinetic resolution of 2-amido secondary benzyl alcohol **3a** was also attempted under the optimal conditions, however, which gave poor s factor. Fortunately, after brief optimizations of the reaction conditions (see Table S1 in SI), highly efficient kinetic resolution of **3a** was achieved under the catalysis of (*R*)-TCYP catalyst (cat **A7**) at 10 °C, with s factor of 31 (Table 4). The substrate scope was also briefly explored, which indicated that secondary benzyl alcohol with an alkyl group was also amenable with the optimal conditions, giving s factor of 21.

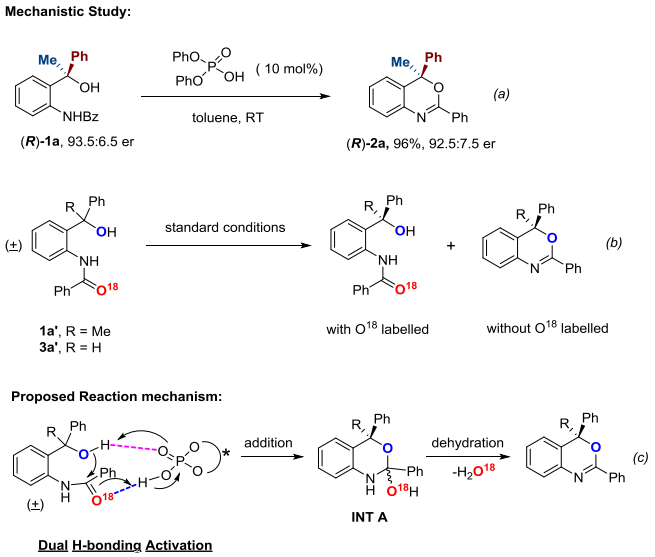
Table 4. Kinetic resolution of secondary benzyl alcohols for the synthesis of chiral 4*H*-3,1-benzoxazines.[a]



[a]Conditions as indicated in Table 2 except 0.02 mmol (*R*)-cat **A7** catalyst was used at 10 °C. [b]At 20 °C.

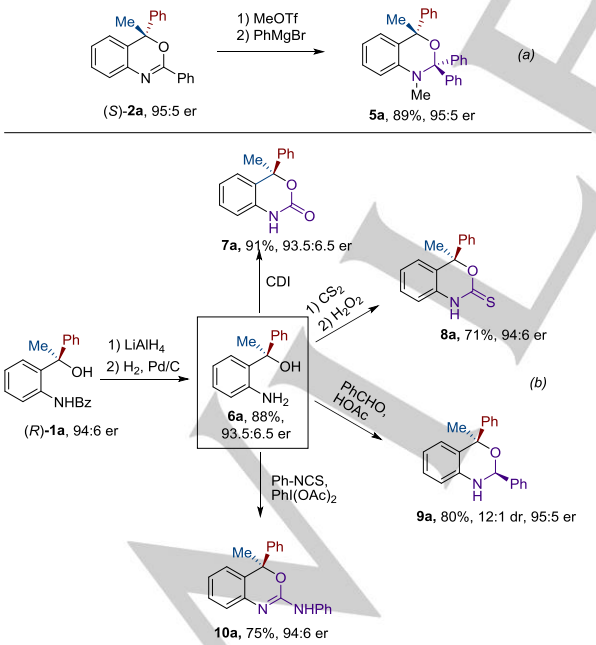
In the reported examples of asymmetric synthesis of 1,3-oxazines through enantioselective cyclization reactions, amide groups reacted as the nucleophiles to attack the "chiral electrophiles"[4-6]. This type of mechanism is also possible in the reactions of kinetic resolution of 2-amido benzyl alcohols, where kinetic resolution was realized through selective ionization of one enantiomer of the racemic benzyl alcohols, and the products were generated through chiral anion mediated addition of amides to carbocation-type intermediates[17] or electrocyclization of *ortho*-quinone methide imine intermediates[11] under CPA catalysis. To shed light on the reaction mechanism of these kinetic resolution reactions, some mechanistic studies were performed. Firstly, treatment of the chiral alcohol (*R*)-**1a** with achiral phosphoric acid catalyst $(PhO)_2POOH$ readily generated (*R*)-4*H*-3,1-benzoxazine **2a** with retained absolute configuration and enantioselectivity, indicating the stereochemistry of product was dominated by the substrate, not the catalyst (Scheme 1, a). Next, treatment of O^{18}-labeled benzamides **1a'** and **3a'** with the standard conditions provided the chiral *4H*-3,1-benzoxaine products without O^{18}-labeling and recovered chiral benzyl alcohols with retained O^{18}-labeling (Scheme 1, b)[16]. Based on these results, a plausible reaction mechanism was proposed, which was distinct from the previous mechanisms using amides as nucleophiles (Scheme 1, c). First, selective dual hydrogen-bonding activation of one enantiomer of the alcohol and amide moiety by CPA catalyst facilitated the addition of hydroxyl group to the amide moiety, generating the orthoester-type intermediate **INT A**. Subsequent facile dehydration of orthoester **INT A** provided the *4H*-3,1-benzoxazine products with the elimination of H_2O^{18}, which may also be mediated by CPA catalyst.

To demonstrate the practicability of these reactions, a gram-scale kinetic resolution of racemic **1a** was performed under the standard conditions, which generated the 4*H*-3,1-benzoxazine **2a** in 49% yield with 95:5 er and recovered (*R*)-**1a** in 51% yield with 94:6 er (see Scheme S1 in SI). It is worth mentioning that the catalyst (*R*)-cat **A8** could be facilely recovered in 89% yield by flash column chromatography. In order to evaluate the synthetic applicability of these reactions, a number of transformations were then carried out. After activation of the C=N bond by treatment of **2a** with MeOTf, nucleophilic addition of PhMgBr provided 2*H*-3,1-benzoxazine derivative **5a** in 89% yield, without erosion of enantioselectivity (Scheme 2, a). $LiAlH_4$ reduction of the benzoyl group followed by hydrogenation using Pd/C as catalyst of (*R*)-**1a** gave the 2-NH_2 benzyl alcohol **6a** in 88% yield, with retained enantioselectivity. With this key chiral



Scheme 1. Mechanistic studies and plausible reaction mechanism.

building block in hand, a number of transformations were readily performed to synthesize a range of chiral heterocycles (Scheme 2, b). Treatment of **6a** with 1,1'-carbonyldiimidazole (CDI) generated 4*H*-3,1-benzoxazine-2-one **7a**, while coupling of **6a** with CS_2 afforded benzoxazine-2-thione **8a**[18]. Condensation of **6a** with benzaldehyde under HOAc catalysis gave the 2*H*-3,1-benzoxazine **9a** in 80% yield with 12:1 dr[19]. Treatment of **6a** with PhNCS in the presence of $PhI(OAc)_2$ facilely gave 2-amino-4*H*-3,1-benzoxazine **10a**[20], which possessed the same core structure of etifoxine.



Scheme 2. Gram-scale reaction and derivatizations of the chiral products.

In conclusion, we have disclosed a novel approach for asymmetric synthesis of 4*H*-3,1-benzoxazines via kinetic resolution of 2-amido benzyl alcohols enabled by chiral phosphoric acid catalysis. A range of benzyl alcohols (including both tertiary and secondary alcohols), N-amide groups and substitutions on the benzene ring are well compatible with the optimal kinetic resolution conditions, producing both 4*H*-3,1-benzoxazine products and recovered 2-amido benzyl alcohols with high enantioselectivities (with s factor up to 94). A plausible reaction mechanism was proposed based on the mechanistic studies, in which the amide groups react as the electrophile. Facile transformations of chiral products into a wide array of potentially biologically active chiral heterocycles well demonstrate the value of these reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: kinetic resolution • 4*H*-3,1-benzoxazines • 2-amido benzyl alcohols • chiral phosphoric acid • organocatalysis

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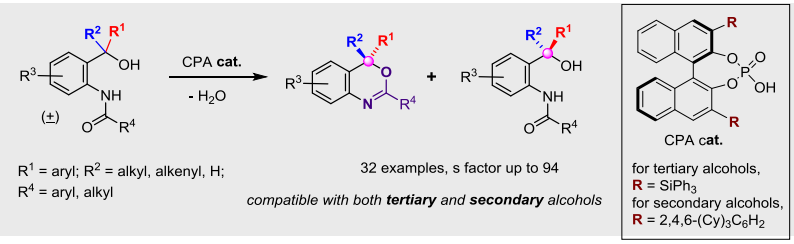

A practical approach for asymmetric synthesis of 4*H*-3,1-benzoxazines was achieved via kinetic resolution of 2-amido benzyl alcohols enabled by chiral phosphoric acid catalysis, with broad substrate scope and high kinetic resolution performances (with s factor up to 94).

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Chiral Phosphoric Acid-Catalyzed Kinetic Resolution of 2-Amido Benzyl Alcohols: Asymmetric Synthesis of 4*H*-3,1-Benzoxazines