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Kinetic Resolution of Tertiary 2-Alkoxycarboxamido-allylic Alcohols by Chiral Phosphoric Acid Catalyzed Intramolecular Transesterification

Subramani Rajkumar[‡], Shunlong He[‡] and Xiaoyu Yang*

Abstract: A highly enantioselective kinetic resolution of tertiary 2-alkoxycarboxamido-allylic alcohols has been achieved through chiral phosphoric acid catalyzed intramolecular transesterification reaction. Both alkyl,aryl- and dialkyl-substituted tertiary allylic alcohols can be well-resolved by the optimal conditions with excellent efficiencies, affording both recovered tertiary alcohols and transesterification products with high enantioselectivities (with s factor up to 164.6). The gram-scale reaction with 1 mol % catalyst loading and facile conversion of chiral products into useful chiral building blocks, such as chiral oxazolidinones and β-amino alcohols, well demonstrated the value of this reaction.

The kinetic resolution of racemic secondary alcohols has been extensively investigated in the past few decades and demonstrated as one of the most efficient and practical approaches to obtain chiral secondary alcohols[1]. In contrast, the corresponding kinetic resolution of tertiary alcohols has been less studied and only a handful of catalytic examples have been reported, including both biocatalytic processes[2] and nonenzymatic methods[3]. However, due to the relative challenging demands for spatial differentiation among three R groups[3a, 3h, 3i] and the intrinsic reaction requirements[3b, 3c], kinetic resolution of tertiary alcohols with high efficiencies that can provide both unreacted starting material and products with high enantioselectivities are still quite limited. Among them, List and co-workers reported chiral Brønsted acid catalyzed kinetic resolution of homoaldols and diols possessing tertiary hydroxyl groups via intra- and intermolecular acetalizations with excellent performance, which could generate both tertiary alcohol starting materials and acetal products with high enantioselectivities[3d, 3f]. Zhao group[3e] and Smith group[3g] reported highly efficient kinetic resolution of tertiary heterocyclic alcohols via asymmetric acylation reactions enabled by NHC catalyst and isothiourea catalyst, respectively. Recently, Oestreich and co-workers developed kinetic resolution of tertiary progargylic alcohols by enantioselective Cu-H-catalyzed Si-O coupling with a broad substrate scope[3j].

Recently, the combination of 2-amidoallylic alcohol substrates (could also be termed as α-hydroxy enamides) with chiral Brønsted acid catalysis has become a useful strategy for asymmetric synthesis of functionalized enamide derivatives[4]. Our group[5] and Kartika group[6] independently reported the asymmetric synthesis of β-indolyl cyclopentenamides from α-hydroxy cyclopentenamides upon chiral phosphoric acid catalysis (Figure 1, a). On the other hand, Chan group reported dehydrative Nazarov-type electrocyclization of α-hydroxy enamides to provide access to chiral 1*H*-indene derivatives under chiral Brønsted acid catalysis[7] (Figure 1, b). In these examples, the chiral anion-paired 2-amidoallyl cations (**INT A**) were proposed as the key intermediates, in which the chiral center from the starting material was eliminated. During our continuous study on asymmetric reactions of α-hydroxy enamides under chiral Brønsted acid catalysis, we recently found that no 2-amidoallyl cation intermediate was generated by treatment of α-hydroxy encarbamates **1** with phosphoric acid catalyst; instead an intramolecular transesterification reaction[8] proceeded smoothly to give the oxazolidinone derivatives **2** (Figure 1, c). Herein, we reported a highly efficient kinetic resolution of tertiary 2-alkoxycarboxamido-allylic alcohols (α-hydroxy encarbamates) by utilizing this reaction under the catalysis of chiral phosphoric acid catalyst[9]. A range of racemic tertiary 2-alkoxycarboxamido-allylic alcohols (including both aryl,alkyl- and alkyl,alkyl-substituted allylic alcohols) could be well resolved by the optimal conditions, generating both transesterification products and unreacted tertiary alcohols with high enantioselectivities. The obtained chiral products could be readily converted into useful chiral building blocks, such as oxazolidinones[10] and β-amino alcohols[11], which have wide applications as chiral auxiliaries, chiral ligands and biologically active molecules.

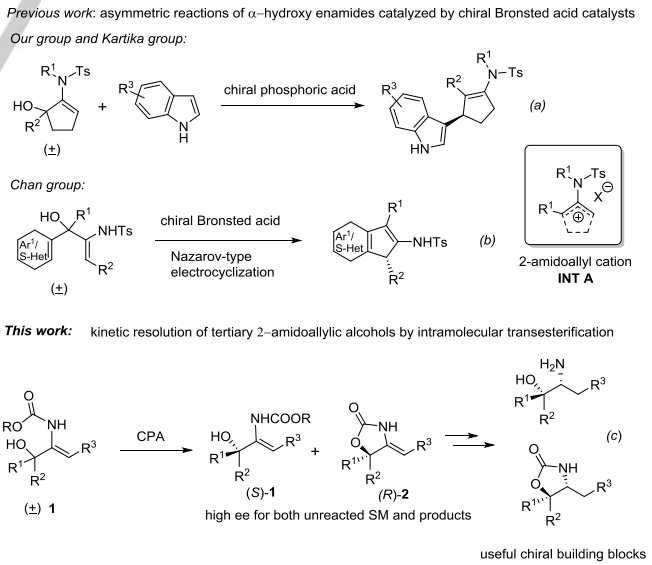

Figure 1. a) Asymmetric addition of indoles to α-hydroxy cyclopentenamides under chiral Brønsted acid catalysis. b) Asymmetric Nazarov-type electrocyclization of α-hydroxy enamides under chiral Brønsted acid catalysis. c) Kinetic resolution of tertiary 2-alkoxycarboxamido-allylic alcohols via chiral phosphoric acid catalyzed intramolecular transesterification.

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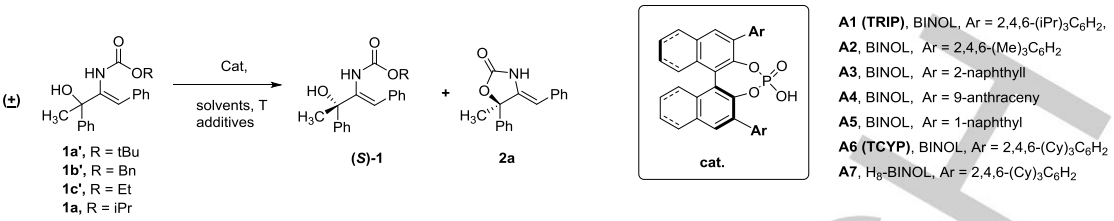
Table 1. Optimization of reaction conditions.[a]



entry	R	T.	cat.	solvents	time	conversion[b] (%)	ee *(S)*-**1**[c] (%)	ee **2a**[c] (%)	***s***[d]
1	*t*Bu	25 °C	**A1**	toluene	64 h	50	60	60	7.2
2	*t*Bu	25 °C	**A2**	toluene	16 h	62	61	37	3.8
3	*t*Bu	25 °C	**A3**	toluene	16 h	45	34	42	3.4
4	*t*Bu	25 °C	**A4**	toluene	16 h	72	97	38	8.1
5	*t*Bu	25 °C	**A5**	toluene	16 h	63	61	36	3.8
6	*t*Bu	25 °C	**A6**	toluene	64 h	54	91	79	26.6
7	*t*Bu	25 °C	**A7**	toluene	64 h	47	70	79	17.7
8	*t*Bu	25 °C	**A6**	DCM	48 h	42	63	87	27.4
9	*t*Bu	25 °C	**A6**	Et_2O	48 h	7	6	78	8.6
10	*t*Bu	25 °C	**A6**	CCl_4	48 h	50	76	75	15.8
11	*t*Bu	25 °C	**A6**	PhCl	48 h	50	87	86	37.5
12	Bn	25 °C	**A6**	PhCl	5 h	64	65	36	3.9
13	Et	25 °C	**A6**	PhCl	2 h	58	90	66	14.5
14	*i*Pr	25 °C	**A6**	PhCl	5 h	54	97	82	41.8
15	*i*Pr	10 °C	**A6**	PhCl	24 h	52	95	89	63.7
16	*i*Pr	0 °C	**A6**	PhCl	48 h	52	98	89	78.4

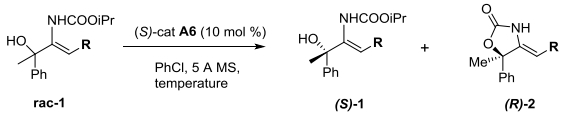
[a]Reactions were run with **1** (0.1 mmol) with catalyst (0.01 mmol, 10 mol %) in solvent (1 mL) with 5 Å molecular sieves (30 mg). [b]Conversion (C) = $ee_s/(ee_s+ee_p)$. [c]Determined by HPLC analysis on a chiral stationary phase. [d]$s = \ln[(1-C)(1-ee_p)]/\ln[(1-C)(1+ee_p)]$.

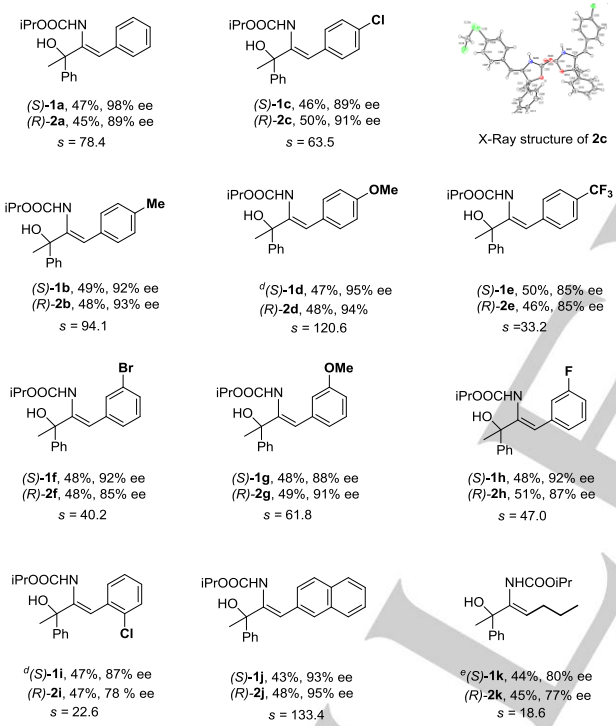
We initiated our studies by using racemic *N*-Boc protected tertiary 2-alkoxycarboxamido-allylic alcohol **1a'** as model substrate and chiral phosphoric acid as catalyst. While using 10 mol % of TRIP catalyst (cat **A1**) in toluene at ambient temperature, the kinetic resolution of tertiary alcohol **1a'** proceeded with a promising selectivity factor (*s*)[12] of 7.2, giving the transesterification product **2a** with 60% enantiomeric excess (ee) and recovered starting material **1a'** with 60% ee (Table 1, entry 1). Subsequently, a variety of BINOL- and H8-BINOL-derived chiral phosphoric acid catalysts were examined (entries 2-7), and the TCYP catalyst (cat **A6**) turned out to be the optimal catalyst, giving the best *s* factor of 26.6 (entry 6). Next, a range of solvents were also explored (entries 8-11), and PhCl was found to be the optimal one, in which the *s* factor could be further improved to 37.5 (entry 11). The leaving groups on the carbamate moiety were also investigated, and we observed that replacing of the tBu group by either Et and Bn substituents led to faster reaction rate, however, with poor kinetic resolution performance as well (entries 12-13). Interestingly, using an iPr group instead of tBu group provided an improved *s* factor of 41.8 and also reduced reaction time (entry 14). With the faster reaction rate found for substrate **1a** at ambient temperature, we further decreased the reaction temperature to 10 °C and 0 °C, and found the *s* factor could be further improved to 63.7 and 78.4 respectively, albeit with longer reaction time (entries 15-16).

With the optimal conditions established, we next sought to investigate the substrate scope of this kinetic resolution reaction. A range of different substitutions at the 3-position of allylic alcohols were firstly evaluated (Table 2). A variety of substituted phenyl groups (bearing different substitutions at the *para*-, *meta*-

and *ortho*-positions) were well tolerated under the optimal conditions, providing the recovered 2-alkoxycarboxamido-allylic alcohols **1** and oxazolidinone derivatives **2** with high enantioselectivities (1**a**-**1i**), as well as a 2-naphthyl group (**1j,** *s* factor = 133.4). The absolute configurations of the products were determined as (*R*) by analogy to product **2c**, whose structure was unambiguously confirmed by X-ray crystallography[13]. A linear alkyl group at the terminal alkene carbon of the allylic alcohol substrate was also compatible with the optimal conditions, albeit providing the products and recovered SM with slightly diminished enantioselectivities (**1k**).

Table 2. Substrate scope regarding to the 3-position of 2-alkoxycarboxamido-allylic alcohols.[a]

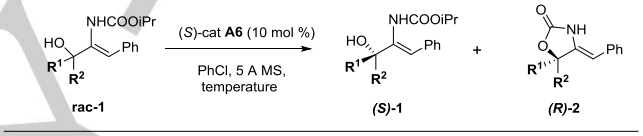


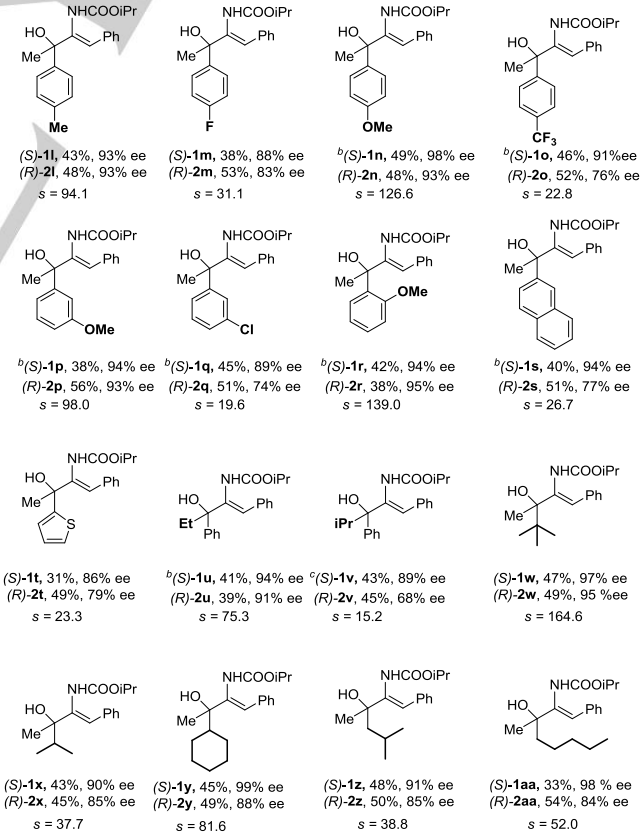


[a]Unless otherwise noted, reactions were performed with 0.2 mmol rac-**1**, 0.01 mmol (*S*)-cat **A6** catalyst and 60 mg 5 Å MS in 2 ml PhCl at 0 °C. The reactions were monitored by HPLC using a chiral stationary phase. [b]The yields are isolated yields. [c]The ee values were determined by HPLC analysis on a chiral stationary phase. [d]These reactions were performed at 10 °C. [e]This reaction was performed at 25 °C.

With the well compatibility of various substitutions at the 3-position of the 2-alkoxycarboxamido-allylic alcohol substrates, we moved our attention to the scope of tertiary alcohol moiety of the substrates (Table 3). Replacing the phenyl group of the tertiary alcohols in **1a** with a range of substituted phenyl groups (with various different substitutions at the *para*-, *meta*- and *ortho*-positions) gave highly efficient kinetic resolution of the 2-alkoxycarboxamido-allylic alcohol substrates (**1l**-**1r**). It's interesting to find that an electron-donating –OMe substitution at different sites of the phenyl groups all gave excellent kinetic resolution performance (**1n**, **1p** and **1r**), with *s* factors > 98. Other aryl and heteroaryl tertiary alcohols were also well tolerated with the optimal conditions (**1s** and **1t**). Other alkyl groups than methyl group were also evaluated. The Et,Ph-substituted substrate (**1u**) still gave high selectivity factor, while the iPr,Ph-substituted substrate (**1v**) gave a decreased *s* factor, probably due to the small size differentiation between these two groups. Tertiary alcohols with two alkyl groups were also investigated under the standard conditions and a range of Me,alkyl-substituted 2-amidoallylic alcohol substrates provided excellent performance under the optimal kinetic resolution conditions. The Me,*t*Bu-substituted allylic alcohol gave the best *s* factor of 164.6 (**1w**), affording both recovered alcohol and cyclized product with > 95% ee. The Me,iPr- and Me,Cy-substituted allylic alcohols were also amenable with the optimal kinetic resolution conditions (**1x** and **1y**). It's surprising to find

Table 3. Substrate scope regarding to the tertiary alcohol moiety of 2-alkoxycarboxamido-allylic alcohols. [a]

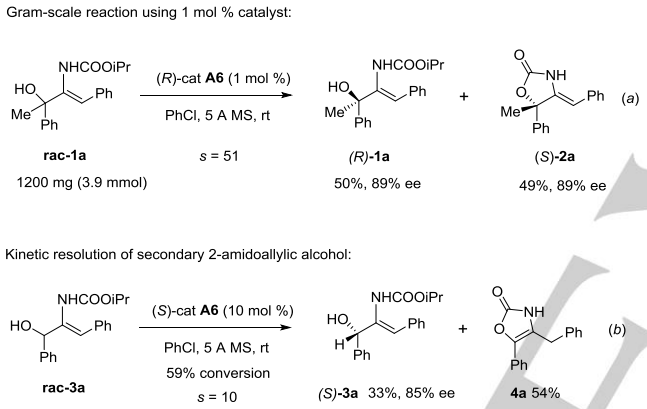




[a]The same conditions as indicated in Table 2. [b]These reactions were performed at 10 °C. [c]These reactions were performed at 25 °C.

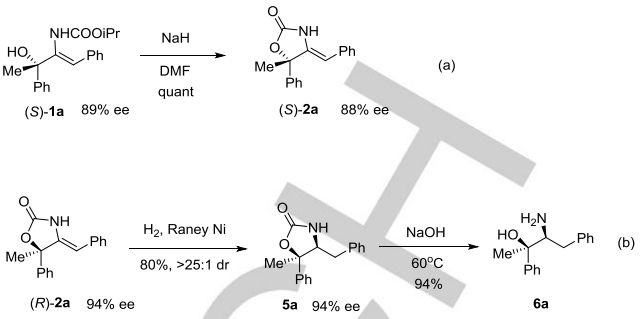
that primary-alkyl,Me-disubstituted allylic alcohols could also be well-resolved by these conditions (**1z** and **1aa**), providing a rare access for the asymmetric synthesis of these tertiary alcohols.

To evaluate the practicability of this kinetic resolution reaction, gram-scale reaction of rac-**1a** was conducted (Scheme 1, a). While performing this reaction at ambient temperature, the catalyst loading of (*R*)-cat **A6** could be further reduced to 1 mol %, still providing comparable *s* factor value and enantioselectivities for (*R*)-**1a** and (*S*)-**2a**. The substrate scope of this kinetic resolution reaction was further extended to secondary 2-alkoxycarboxamido-allylic alcohol substrate (Scheme 1, b). With racemic secondary alcohol **3a** used as substrate, the kinetic resolution with the same conditions proceeded smoothly to provide (*S*)-**3a** in 33% isolated yield with 85% ee without optimization, with selectivity factor of 10. However, under these standard conditions, the transesterification product underwent further isomerization to give 2-oxazolone **4a** as product, with the chiral center eliminated.



Scheme 1. Gram-scale reaction and kinetic resolution of secondary 2-alkoxycarboxamido-allylic alcohol.

To demonstrate the utility of this reaction, the derivatizations of the chiral products were also studied. Base promoted cyclization of (*S*)-**1a** readily yielded (*S*)-oxazolidinone **2a**, thus providing an enantiodivergent route for the asymmetric synthesis of both enantiomers of **2a (**Scheme 2, a**)**. Hydrogenation of oxazolidinone **2a** with Raney Ni as catalyst afforded oxazolidinone **5a** in 80% yield with > 25:1 dr without erosion of the enantioselectivity, which could be used as chiral auxiliaries in asymmetric synthesis[10]. The relative configuration of compound **5a** was determined by NOE analysis[13]. Further hydrolysis of **5a** with aqueous NaOH solution cleanly removed the protecting group, affording free β-amino alcohol **6a** in high yield (Scheme 2, b).



Scheme 2. Derivatizations of the chiral products.

In conclusion, we have disclosed a highly efficient kinetic resolution of tertiary 2-alkoxycarboxamido-allylic alcohols via intramolecular transesterification reaction under the catalysis of chiral phosphoric acid catalyst. A rang of different tertiary alcohols, including aryl,alkyl- and alkyl,alkyl-disubstituted 2-alkoxycarboxamido-allylic alcohols are well-compatible with the optimal kinetic resolution conditions, providing access to both unreacted tertiary alcohols and cyclized oxazolidinone products with high enantioselectivities. The gram-scale reaction with reduced catalyst loading and facile transformation of the chiral products into useful chiral building blocks well demonstrated the potential of this method.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: kinetic resolution • tertiary alcohols • 2-alkoxycarboxamido-allylic • chiral Brønsted acid• transesterification

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[13] For details see Supporting Information.

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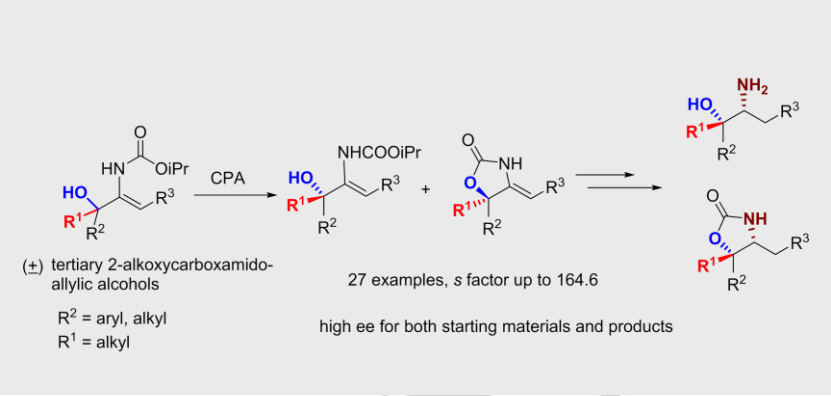

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A highly enantioselective kinetic resolution of tertiary 2-alkoxycarboxamido-allylic alcohols has been achieved through chiral phosphoric acid catalyzed intramolecular transesterification reaction. Both alkyl,aryl- and dialkyl-substituted tertiary allylic alcohols can be resolved with excellent efficiencies, with *s* factor up to 164.6. This method affords expedient access to enantioenriched oxazolidinones and β-amino alcohols.