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Kinetic Resolution of 2-*N*-Acylamido Tertiary Allylic Alcohols: Asymmetric Synthesis of Oxazolines

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Abstract. A series of cyclohexyl-fused SPINOL-derived phosphoric acids (Cy-SPA) have been developed to catalyze the kinetic resolution of 2-*N*-acylamido tertiary allylic alcohols, providing access to chiral oxazolines bearing C-2 alkyl substituents with high enantioselectivities (with *s*-factors up to 153). Gram-scale reaction with 1 mol% catalyst loading and transformations of the chiral products demonstrates the value of these methods.

Keywords: Asymmetric catalysis; Organocatalysis; Kinetic resolution; Alcohols; Oxazolines; Novel spirocyclic phosphoric acids

Chiral tertiary alcohols and their derivatives are ubiquitous among a variety of bioactive natural products and pharmaceuticals, however, their efficient asymmetric catalytic synthesis remains a significant challenge. The most straightforward strategy, namely asymmetric additions of carbon-centered nucleophiles to ketones[1], faces the challenges of less reactivity and decreased enantioface differentiation of ketone substrates and the vulnerability of tertiary alcohol products under harsh conditions. Kinetic resolution (KR) is one of the most reliable and practical method to produce enantioenriched products[2], and numerous asymmetric catalytic methods have been developed for kinetic resolution of secondary alcohols, both through enzymatic and non-enzymatic catalysis. Analogously, the kinetic resolution of tertiary alcohols is also much more challenging due to the demand for spatial differentiation between three R groups[3]. Nonetheless, several elegant methods for kinetic resolution of tertiary alcohols via asymmetric hydroxy-protection reactions have been developed, including the asymmetric acylation by Miller group[4], Zhao group[5] and Smith group[6], asymmetric silylation by Oestreich group[7] and asymmetric benzoylation by Maruoka group[8], albeit with relatively limited scope (Figure 1, a). On the other hand, the asymmetric intramolecular-type cyclization is another powerful method for kinetic resolution of tertiary alcohols, which can produce chiral heterocycles bearing quaternary stereocenters simultaneously. List group developed ingenious kinetic resolution of tertiary alcohols via asymmetric acetalizations[9]. Our group realized the kinetic resolution of tertiary 2-alkoxycarboxamido allylic alcohols[10] and 2-amido benzyl alcohols[11] enabled by chiral phosphoric acid catalyzed intramolecular cyclizations, generating chiral oxazolones and 4H-3,1-benzoxazines (Figure 1, b).

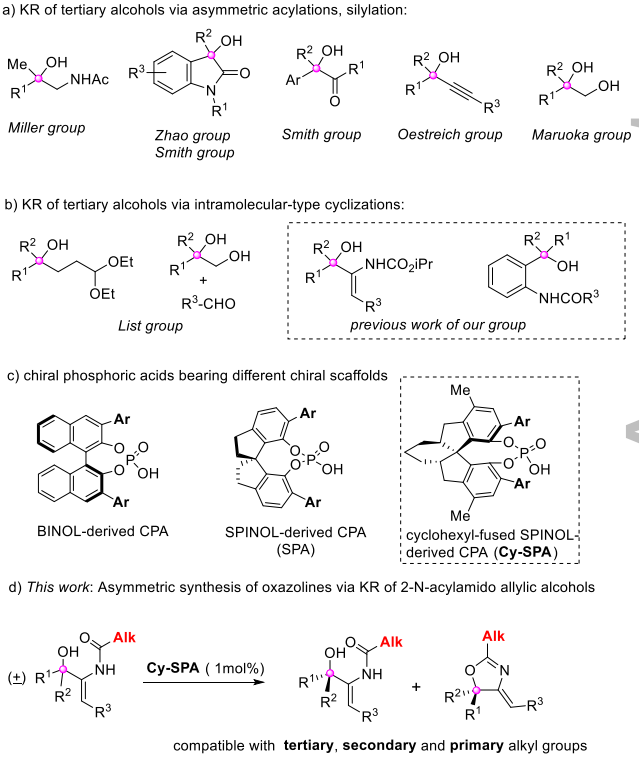

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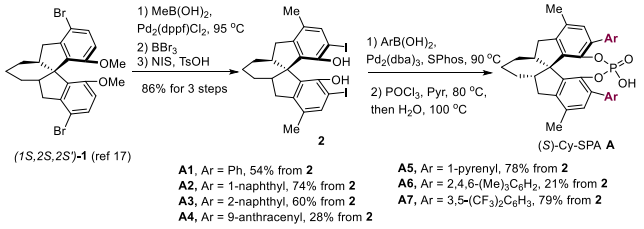
Figure 1. Asymmetric catalytic synthesis of oxazolines.

Since the pioneer work of Akiyama and Terada on using BINOL-derived chiral phosphoric acid (CPA) catalysts[12] in asymmetric catalysis, last 15 years have witnessed the tremendous development in the field of CPA catalysis[13]. Alongside with the *ortho*-substitutions of CPA catalysts, the chiral scaffolds also played important roles in controlling the enantioselectivities of these reactions. Thus, a variety of chiral diol scaffolds have been utilized for construction of CPA catalysts[14], and among which the SPINOL-derived phosphoric acid (SPA) catalyst[15] exhibited excellent performances in a series of asymmetric reactions (Figure 1, c)[16]. However, the traditional synthetic route to chiral SPA still suffered the tedious synthetic steps and requirements of resolution using stoichiometric amount of chiral reagents[17]. Consequently, the development of highly efficient asymmetric catalytic synthesis of novel SPA[18] is still highly demanding. With our continuous interest on kinetic resolution of tertiary alcohols and novel asymmetric reactions of amido allylic alcohols[19], herein we describe the kinetic resolution of 2-*N*-acylamido tertiary allylic alcohols via intramolecular dehydrative condensation enabled by novel cyclohexyl-fused SPINOL-derived phosphoric acids (Cy-SPA), generating chiral oxazolines bearing C-2 alkyl groups, which is also a type of challenging oxazoline products to be accessed via the known asymmetric catalytic approaches[20] (Figure 1, d).

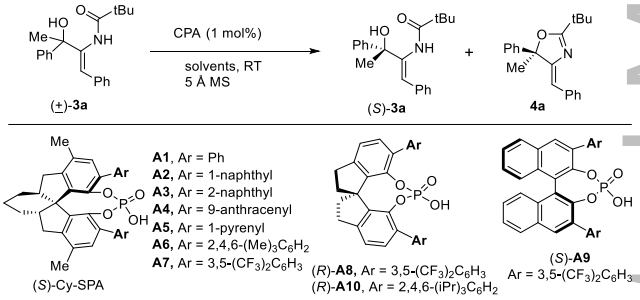
Recently, Ding and co-workers reported a highly efficient method for asymmetric catalytic synthesis of chiral cyclohexyl-fused SPINOLs via enantioselective hydrogenations[21], which we envisioned would be an idea starting material for asymmetric synthesis of novel SPAs[22]. With this idea in mind, we started our study by Suzuki coupling of the known cyclohexyl-fused SPINOL derivative **1** (99% ee) with $MeB(OH)_2$, which was followed by deprotection of the O-Me groups and *ortho*-iodination to provide the di-iodinated product **2** with high efficiency (86% for 3 steps, Scheme 1). With this key intermediate **2** in hand, a range of aryl boronic acids were then coupled under Suzuki coupling conditions to give the corresponding diols, which were converted to Cy-SPAs **A1-7** via phosphoration and subsequent hydrolysis.



Scheme 1. Synthesis of chiral cyclohexyl-fused SPINOL-derived phosphoric acids. dppf = 1,1'-Bis(diphenylphosphino)ferrocene, SPhos = 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl.

We initiated our kinetic resolution study by choosing 2-*N*-Piv substituted tertiary allylic alcohol **3a** as model substrate. Treatment of racemic **3a** with Cy-SPA catalyst **A1** (1 mol%) and activated 5 Å molecular sieves (MS) at room temperature for 5 hours provided the oxazoline **2a** with 83% ee and recovered **3a** with 41% ee, giving a selectivity factor of 8.4[23] (Table 1, entry 1). Subsequently, the synthesized Cy-SPA catalysts were screened in this reaction (entries 2-7). Encouragingly, the 3,5-bis(trifluoromethyl)phenyl substituted catalysts **A7** provided the best kinetic resolution performances, giving *s*-factor of 98, and clean reaction system as well (entry 7). Switching the chiral scaffold of **A7** to SPINOL-type (CPA **A8**) halved the *s*-factor to 49 (entry 8), while switching the chiral scaffold to BINOL-type (CPA **A9**) only provided the *s*-factor of 4.1 (entry 9). The sterically bulky CPA catalyst **A10** was also investigated in this reaction, however, which generated significant amount of byproduct in this reaction, albeit still giving the recovered SM and product with high enantioselectivities (entry 10). Next, a range of solvents were examined in this reaction, which indicated toluene still as the optimal solvent (entries 11-14). Further decreasing the reaction temperature to 10 °C provided the optimal kinetic resolution conditions, under which an improved *s*-factor of 126 was obtained (entry 15).

Table 1. Optimization of reaction conditions.



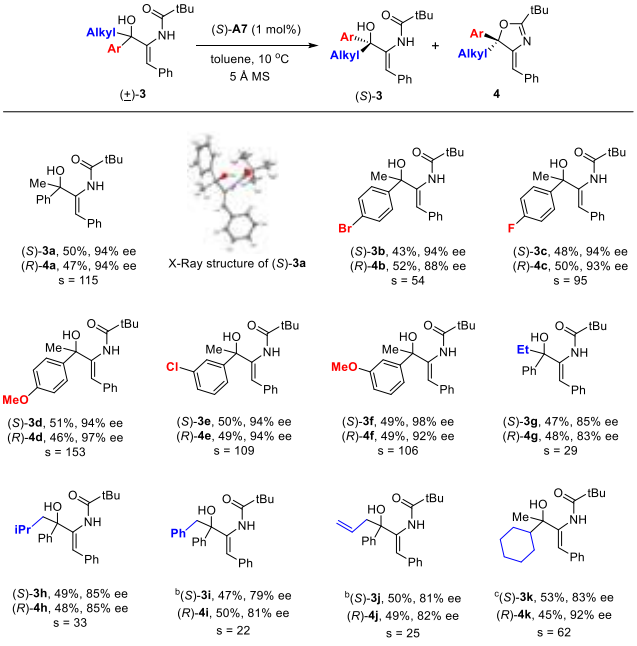
entry	cat	solvents	time (h)	ee_s[b] (%)	ee_p[b] (%)	C[c] (%)	*s*[d]
1	**A1**	Tol	5	41	83	37	8.4
2	**A2**	Tol	1	90	86	51	42
3	**A3**	Tol	1	26	86	26	8.6
4	**A4**	Tol	0.5	83	84	48	49
5	**A5**	Tol	0.5	99	68	58	30
6	**A6**	Tol	1	55	86	40	18
7[e]	**A7**	Tol	1	94	93	50	98
8[e]	**A8**	Tol	1	-95	-86	52	49
9[e]	**A9**	Tol	7	-38	-48	44	4.1
10[f]	**A10**	Tol	3	-94	-91	51	81
11[e]	**A7**	DCM	1	73	82	47	22
12[e]	**A7**	$CHCl_3$	1	30	93	24	37
13[e]	**A7**	CCl_4	1	63	93	40	53
14[e]	**A7**	Et_2O	8	94	90	51	67
15[e,g]	**A7**	Tol	5	99	92	52	126

[a]Reactions were performed with **3a** (0.1 mmol), CPA (0.001mol, 1 mol%) in solvents (1 mL) with 5 Å MS (40 mg) at room temperature for designated time. [b]Ee values

were determined by HPLC analysis on a chiral stationary phase. [c]Conversion were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]s = ln[(1-C)(1-ee$_s$)]/ln[(1-C)(1+ee$_s$)]. [e]Conversions were determined by C = ee$_s$/(ee$_s$+ee$_p$). [f]With 5 mol% catalyst. [g]At 10 °C.

With the optimal kinetic resolution conditions in hand, we first examined the scope of various substituents at the 1-position of 2-*N*-Piv substituted tertiary allylic alcohols (Table 2). A series of *para*- and *meta*-substituted phenyl groups were well tolerated at the 1-position of allylic alcohols, regardless of the electronic nature of substituents (**3b-3f**). The absolute configurations of the products were assigned by analogy to (*S*)-**3a**, whose absolute structure was unambiguously determined by X-Ray crystallography[24]. Next, a variety of alkyl groups at the 1-position of allylic alcohols were also examined in this reaction, which were also amenable with the optimal condition (**3g-3j**), including the benzyl group (**3i**) and allyl group (**3j**), albeit with a bit diminished *s*-factors. Finally, an 1,1-dialkyl substituted 2-amido allylic alcohol substrate **3k** was also investigated under the standard kinetic resolution conditions, which was also well resolved, giving *s*-factor of 62 (**3k**).

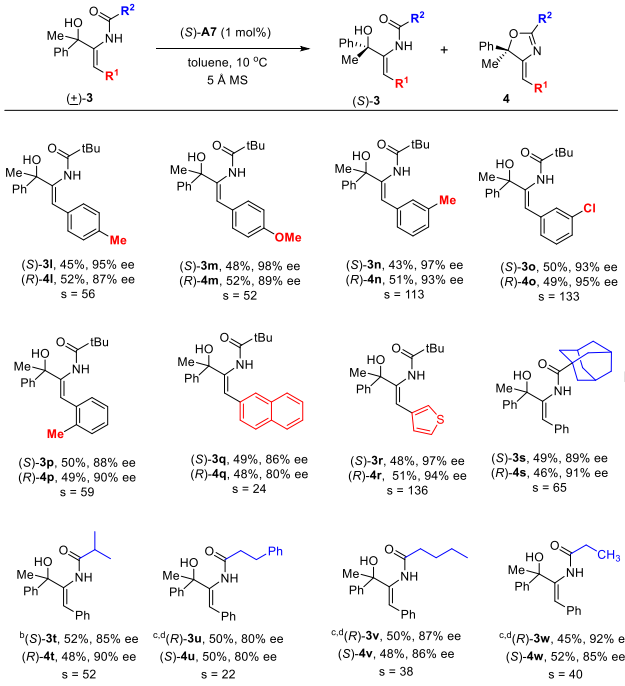
Table 2. Scope for kinetic resolution of 2-amido tertiary allylic alcohols regarding to variants at the 1-position.



[a]Reactions were performed with **3** (0.2 mmol), (*S*)-**A7** (0.002 mol, 1 mol%) in toluene (2 mL) with 5 Å MS (80 mg) at 10 °C. Yields were isolated yields. Ee values were determined by HPLC analysis on a chiral stationary phase. s = ln[(1-C)(1-ee$_s$)]/ln[(1-C)(1+ee$_s$)]. C = ee$_s$/(ee$_s$+ee$_p$). [b]With (*S*)-**A7** (0.01 mmol, 5 mol%). [c]At -20 °C.

The scope for variants at the 3-position of racemic tertiary allylic alcohols were also studied (Table 3). A series of substituted phenyl groups were compatible with the optimal conditions, including various *para*-, *meta*- and sterically demanding *ortho*-substituted phenyl groups (**3l-3p**). The naphthyl group (**3q**) and the heteroaryl group (**3r**) were also well tolerated at this position. Next, the scope for alkylacyl groups at the 2-*N*-position of allylic alcohol substrates was examined. The bulky 1-adamantanyl group was amenable substituent, giving *s*-factor of 65 (**3s**). The less bulky alkyl substituted 2-oxazolines were relatively challenging products for asymmetric catalytic synthesis according to previous reports[20m, 20n]. Encouragingly, kinetic resolution of a secondary alkylacyl substituted 2-amido allylic alcohols under the standard conditions proceeded smoothly to give the product **4t** with 90% ee and recovered SM with 85% ee. Furthermore, the primary alkylacyl substituted 2-amido allylic alcohols could be kinetically resolved with high *s*-factors as well, albeit the SPINOL-derived 2,4,6-triisopropylphenyl substituted CPA (*R*)-**A10** (5 mol%) was used instead (**3u-3w**).

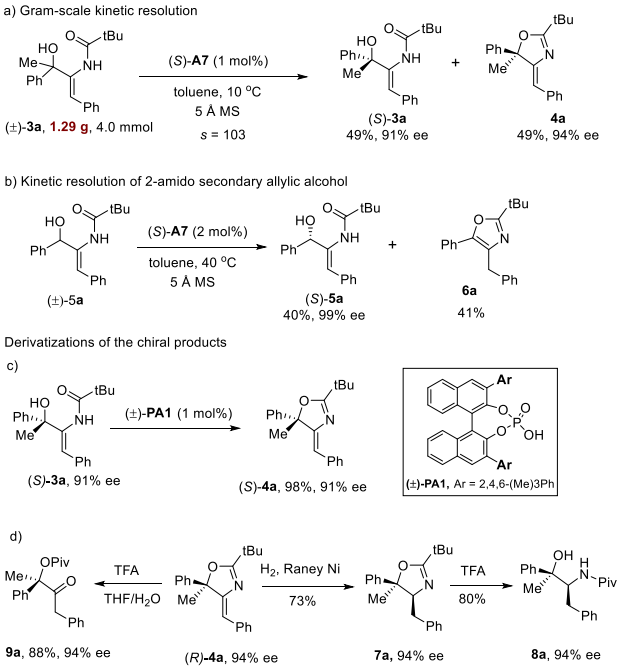
Table 3. Scope for kinetic resolution of 2-amido allylic alcohols regarding to variants at the 3- and 2-N positions.



[a]Reactions were performed with the same conditions as indicated in Table 2. [b]At -20 °C. [c]With (*R*)-**A10** (0.01 mmol, 5 mol%). [d]At 0 °C.

To demonstrate the practicability of this method, kinetic resolution of 4.0 mmol of racemic **3a** (1.29 g) under the standard condition was performed, which provided the (*S*)-**3a** in 49% yield with 91% ee and **4a** in 49% yield with 94% ee, with an *s*-factor of 103 (Scheme 2, a). Kinetic resolution of the racemic 2-amido secondary allylic alcohol **5a** was also studied, which provided the (*S*)-**5a** in 40% yield with 98% ee; however, oxazoline **6a** was isolated as the major product, with the chiral center eliminated via double bond isomerization (Scheme 2, b). To showcase the applicability of these methods, the derivatizations of the chiral products were also conducted. Treatment of

the (*S*)-**3a** with racemic phosphoric acid catalysts **PA1** (1 mol%) readily provided the oxazoline (*S*)-**4a** in 98% yield with retained enantiomeric excess, providing important insight on the reaction mechanism, in which the hydroxy group played as the nucleophile and the amide moiety as the electrophile under the promotion of CPA catalyst (Scheme 2, c)[11]. Hydrogenation (1 atm) of (*R*)-**4a** using Raney Ni as catalyst gave the oxazoline product **7a** in 73% yield, with >25:1 dr, which underwent the hydrolysis in the presence of TFA to afford the β-amino tertiary alcohol **8a** in 80% yield with 94% ee (Scheme 2, d). Additionally, direct hydrolysis of oxazoline (*R*)-**4a** in the presence of TFA and H_2O readily afforded the α-hydroxy ketone **9a**, without diminishment of enantioselectivity.



Scheme 2. Gram-scale reaction, kinetic resolution of 2-amido secondary allylic alcohol and derivatizations of chiral products.

In conclusion, we have disclosed an efficient protocol for kinetic resolution of 2-*N*-acylamido tertiary allylic alcohols enabled by a type of novel spirocyclic phosphoric acids (Cy-SPA) catalysts, generating 2-alkyl-substituted oxazolines with high stereoselectivities. A series of variants were well tolerated at the 1- and 3-positions of the 2-amido allylic alcohols, as well as various alkylacyl groups at the 2-*N*-position, which gave *s*-factors up to 153. Gram-scale reaction with low catalyst loading (1 mol%) and facile transformations of the chiral products demonstrate the synthetic potential of these methods.

Experimental Section

To a 4 mL vial containing a stirring bar was added racemic **3** (0.2 mmol) and activated 5 Å MS (80 mg). After adding toluene (2 mL) via syringe and cooling to 10 °C, a solution of (*S*)-**catA7** (1.6 mg, 1 mol%) in toluene (0.1 mL) was added slowly. After achieving suitable conversion as monitored by chiral HPLC analysis, the reaction mixture was quenched by adding Et_3N (10 uL) and resulting mixtures was purified by column chromatography to give the recovered (*S*)-**3** and product **4**.

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Kinetic Resolution of 2-*N*-Acylamido Tertiary Allylic Alcohols: Asymmetric Synthesis of Oxazolines

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