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Chiral Silver Phosphate-Catalyzed Cycloisomeric Kinetic Resolution of α-Allenic Alcohols

Yan Wang, Kuan Zheng, and Ran Hong*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

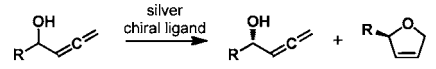
ABSTRACT: A kinetic resolution of α-allenic alcohols is realized through chiral silver phosphate-catalyzed cycloisomerization with high stereoselectivity (selectivity factor up to 189) and tolerance of a variety of functional groups. A mechanistic model is proposed to interpret the origin of the high stereoselectivity and broad substrate scope.

Among transition metals involved in chemical reactions with allenes, gold has shown incredible reactivity in the past decade.[1] A seminal work on gold-catalyzed asymmetric cycloisomerization of allenes was recently orchestrated by the Toste group.[2] The concept of anion metathesis was particularly remarkable in utilizing chiral silver phosphate to synthesize the gold catalyst that exhibits excellent enantioselectivity in the cyclization of allenic alcohols or amines. However, the silver salt itself could not promote the transformation with considerable enantioselectivity. Despite the success of silver-catalyzed cyclization reactions of allenic alcohols and decades of research[3] since the first report in 1974,[4] enantioselective silver-catalyzed cycloisomerization remains elusive.

Recent progress on the chemistry of α-allenic alcohols underlines that they can be readily and stereoselectively converted into versatile functional groups.[5] Methods for the construction of chiral α-allenic alcohols by coupling of propargylic reagents with carbonyl groups have been limited to three categories: (1) stoichiometric chiral reagents, such as chiral tin and borane reagents;[6] (2) catalytic chiral Lewis base-activated silane reagents;[7] and (3) transition-metal-catalyzed asymmetric allenylation.[8] These conditions always suffer from limited substrate scope, complicated reaction systems, and multiple-step syntheses needed for the preparation of chiral ligands. Enzymatic kinetic resolution has given excellent enantioselectivities for the substrates that have been tested, but the special steric and electronic requirements during preorganization in the active site of an enzyme leave problems for late-stage transformations.[9] Moreover, the straightforward asymmetric reduction of allenone seems far from general for practical use in organic synthesis.[10,11] A practical method with broad compatibility and excellent enantioselectivity for a variety of functional groups is still needed.

During the biomimetic synthesis of stemoamide, the α-allenic alcohol derived from the iminium ion-initiated cyclization was eventually converted into the desired butenolide.[12] We applied a silver-promoted cyclization of the α-allenic alcohol to deplete one stereoisomer on the basis of conformational strain. Encouraged by this phenomenon, we envisioned that a silver−chiral ligand system may preferentially promote the cyclization of one stereoisomer of an α-allenic alcohol through cycloisomerization in a general sense (Scheme 1). According to this strategy, the cycloisomeric kinetic resolution of α-allenic alcohols (*rac*-**1**) would deliver 2,5-dihydrofurans (**2**)[15] and recovered starting material **1** with excellent enantioselectivities. Herein we report experimental results to prove the concept.

Scheme 1. Kinetic Resolution of α-Allenic Alcohols



To begin the study, phenyl-2,3-allen-1-ol (*rac*-**1a**) was chosen as a model substrate for the asymmetric silver-catalyzed kinetic resolution, since the resulting products **1a** and 2-phenyl-2,5-dihydrofuran (**2a**) are well-documented in a variety of synthetic methods in the literature.[6−8,9a,13] Although Marshall's protocol ($AgNO_3/CaCO_3$)[12] could promote the cyclization of **1a**, when bisoxazoline **4a** was added, no product was detected even after 3 days at room temperature (Table 1, entry 1). The gold triflate expected after anion metathesis did not give any conversion in the presence of ligand **4a** with the combination of gold chloride and silver triflate (entry 2). When we turned to silver complexes, representative chiral ligands such as chiral bisoxazolines **4a** and **4b**, salen-type diimines **5** and **6**, BINAP (**7**), and monodentate phosphoramidite (MonoPhos) **8** were screened with different silver salts ($AgNO_3$ and AgOTf), all of which gave low levels of enantioselectivity for dihydrofuran **2a** and recovered allenic alcohol **1a** (entries 3−8). Recently, sporadic examples of chiral silver catalysts that promote novel reactions have appeared,[14] but the catalytic power of chiral silver phosphate is largely underestimated. To our delight, when chiral silver phosphate **9a** was screened, **1a** was recovered with 66% ee and **2a** was isolated with 35% ee (entry 9). Next, several 3/3′-substituted chiral phosphates were examined. Biphenyl-substituted phosphate **9c** gave a selectivity factor (*s*) of 43.4 (entry 11). Although **9d** gave a similar level of selectivity as **9c**, further optimization was abandoned because of the lower conversion and ee (entry 12). The low efficiency of in situ-generated gold phosphate[2] indicates the exclusive role of silver phosphate (entry 13). A variety of solvents (tetrahy-

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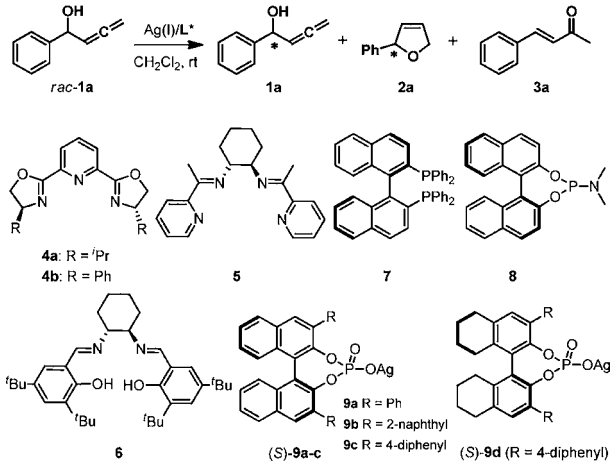
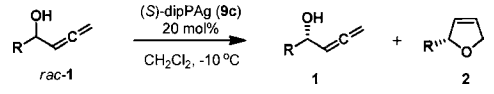
Table 1. Ligand Screening for Catalytic Kinetic Resolution of α-Allenic Alcohol *rac*-1a



entry	catalyst	Ligand	time (h)	conv. (%)	ee of 1a (%)[a]	ee of 2a (%)[a]	2a/3a
1[b]	$AgNO_3$ (1.0 equiv) $CaCO_3$ (1.0 equiv)	**4a**	72	trace			
2[c]	AgOTf (5 mol%) Ph_3PAuCl (5 mol%)	**4a**	6	trace			
3	AgOTf (20 mol%)	**4a**	22	20	0	5	2:1
4	AgOTf (20 mol%)	**4b**	22	17	< 3	13	3.6:1
5	AgOTf (20 mol%)	**5a**	27	trace			
6[d]	AgOTf (20 mol%)	**5b**	27	34	< 3	< 3	**2a**
7	AgOTf (20 mol%)	**7**	96	20	3	5	**2a**
8[d]	AgOTf (20 mol%)	**8**	120	5	< 3	16	1:1
9	**9a** (20 mol%)		6.5	57	66	35	**2a** (5.7)[e]
10	**9b** (20 mol%)		4	57	42	21	**2a** (2.8)[e]
11	**9c** (20 mol%)		4	54	97	70	**2a** (43.4)[e]
12	**9d** (20 mol%)		8	36	52	82	**2a** (42.7)[e]
13	dppm$(AuCl)_2$ (2.5 mol%) **9c** (5 mol%)		3.5	45	10	7	**2a** (1.4)[e]

[a]The ee's were determined by chiral HPLC. [b]1 equiv of chiral ligand was used. [c]5 mol % ligand was used. [c]PhMe was used as the solvent. [e]The selectivity factor (*s*) given in parentheses was calculated as $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$. *C* represents conversion.

Table 2. Substrate Scope for Aryl-Substituted α-Allenic Alcohols



substrate	time (h)	conv. (%)	ee % (1) (yield)[a]	ee % (2) (yield)[a]	*s*
1a	31	49	88 (48%)	85 (48%)	66
1b	248	49	82 (49%)	n.d. (45%)[b]	32
1c	46	44	75 (54%)	90 (43%)	97
1d	46	52	83 (46%)	89 (51%)	28
1e	48	54	94.5 (44%)	n.d. (52%)[b]	33
1f	48	56	99.0 (39%)	n.d. (49%)[b]	41
1g	56	53	83 (50%)	n.d. (51%)[b]	17
1h	144	37	53 (55%)	84 (37%)	33
1i	144	53	97 (44%)	84 (51%)	55
1j	47	53	97 (45%)	82 (53%)	55
1k	46	53	93 (47%)	83 (53%)	35

[a]Isolated yields are given in parentheses; the ee's were determined by chiral HPLC. [b]n.d. = not determined.

drofuran, acetone, dimethoxyethane, acetonitrile, and *tert*-butyl methyl ether) were screened, but none of these gave better results than nonpolar solvents such as dichloromethane, 1,2-dichloroethane, and toluene [Table S2 in the Supporting Information (SI)].

With a proper chiral catalyst found in the preliminary screening (Table 1, entry 11), the catalyst loading and reaction temperature were also examined. Decreasing the catalyst loading dramatically affected the reaction rate, and a significant drop of selectivity was observed (Table S4, entries 2 and 3 vs entry 1). Decreasing the reaction temperature to −10 °C clearly gave better selectivity (*s* increased from 43.4 to 66.3; entry 5 vs 1), but a further decrease to −20 °C gave a sluggish reaction and low conversion within a comparable time (entry 6).

We next investigated the scope of substrates for cycloisomeric kinetic resolution by the aforementioned optimal reaction conditions of chiral silver phosphate (*S*)-dipPAg (**9c**). First, a variety of substituents on the aromatic ring were investigated (Table 2). Both electron-deficient and electron-rich substituents gave excellent selectivities (*s* = 17−97). Although several recovered starting materials did not reach 90% ee (**1b**, **1c**, **1d**, **1g**, and **1h**), given by higher *s* factors, high ee's of α-allenic alcohol and 2,5-dihydrofuran could be obtained when the conversion is slightly above or below 50%, depending on the desired product. For instance, when the conversion of **1c** was only 44%, the allenic alcohol was recovered in 54% yield with 75% ee, while dihydrofuran **2c** was isolated in 43% yield with 90% ee; for this substrate, *s* = 97. Moreover, ortho-substituted **1i** and **1j** gave impressive selectivities (*s* = 55), and the allenic alcohols were recovered in 44−45% yield with 97% ee, although the substrate bearing an electron-deficient substituent required a longer reaction time (144 h vs 47 h). Finally, naphthalene-bearing substrate **1k** could be accessed with high enantiopurity (93% ee, 47% yield, *s* = 35). Its corresponding cyclized product **2k** was obtained with 83% ee in 53% yield.

The uniformly excellent levels of asymmetric induction with aryl-substituted substrates encouraged us to examine alkyl- and alkenyl-substituted allenic alcohols (Table 3). To our delight, a

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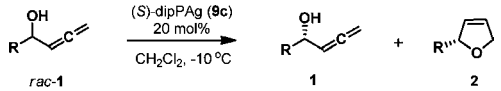
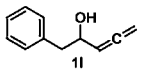
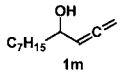
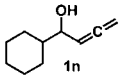
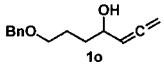
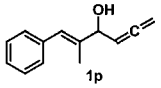
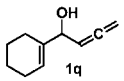
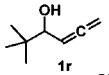
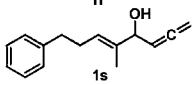
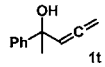
Table 3. Substrate Scope for Alkyl- and Alkenyl-Substituted α-Allenic Alcohols



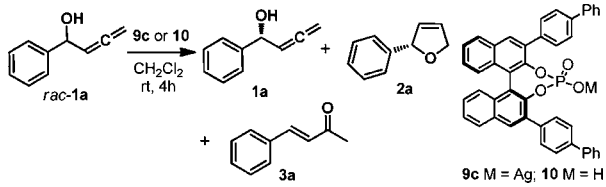
substarte	time (h)	conv. (%)	ee% (1) (yield)[a]	ee% (2) (yield)[a]	s
 1l	37	54	92 (46%)	70 (46%)	27
	51	58	98.3 (35%)	69 (53%)	26
 1m	28	58	97 (41%)	65 (55%)	23
	21	48	77 (50%)	79 (44%)	25
 1n	70	58	99.8 (40%)	67 (57%)	48
 1o	48	68	96.8 (31%)	41 (64%)	10
 1p	47	51	93 (45%)	90 (50%)	60
 1q	28	51	97.7 (48%)	93.2 (45%)	189
 1r	106	56	99.6 (30%)	n.d. (25%)[b]	49
 1s	51	54	97.6 (42%)	90 (49%)	47
 1t	18.5	52	62 (48%)	45 (52%)	6.8[c]

[a]Isolated yields are given in parentheses; the ee's were determined by chiral HPLC (see the SI for details). [b]n.d. = not determined; compound **2r** is extremely volatile. [c]The reaction was run at room temperature.

majority of these substrates underwent the kinetic resolution with a higher reaction rate and equally high enantioselectivities. For typical alkyl substituents such as benzyl (**1l**), *n*-heptyl (**1m**), and cyclohexyl (**1n**) groups, excellent selectivities were observed, and the alkylated allenic alcohols were recovered in good yields (35−50%) with outstanding asymmetric induction (92.0−99.8% ee). More interestingly, although resolution of **1o** bearing a functionalized alkyl chain gave moderate selectivity (*s* = 10), compound **1o** was still isolated with 96.8% ee after 48 h. The enantiomerically enriched **1o** would allow further elaboration to afford some key intermediates in natural product synthesis. Alkenylated substances **1p−s** exhibited even better selectivity than alkylated ones. For **1p** and **1q**, both products were obtained with over 90% ee, and **1q** gave the highest selectivity factor in this study (*s* = 189). The sterically bulky *tert*-butyl group was tolerated, and **1r** was obtained with 99.6% ee, although the reaction was little slow. Particularly noteworthy is the kinetic resolution of tertiary alcohol **1t**. In view of its steric crowdedness at C(1) and the fact that it is inaccessible by known enzymatic resolution and asymmetric catalytic alkenylation, the impressive selectivity (*s* = 6.8) shows the unprecedented power of this approach for asymmetric induction.

Chiral phosphoric acid has been rapidly recognized as a privileged organic catalyst in the past several years since its renaissance by the Akiyama and Terada groups.[15] Very recently, several groups have revealed that metal salt contaminations have a profound effect in some cases.[16] We thus designed several experiments to ascertain the catalytic species in our catalytic system. Chiral phosphoric acid alone preferentially promoted the isomerization to give enone **3a** as the sole product in 17% isolated yield, and the recovered **1a** was isolated in 75% yield with 4.7% ee (*s* = 1.4; Table 4, entry 3). Silver

Table 4. Verification of Chiral Silver Phosphate



entry	cat. (mol%)	conv.(%)	product	ee% (1a)	ee% (2a)	s
1	**9c** (20)	54	**1a**+**2a**	97	70	43.4
2	Ag_2CO_3 (10)	trace				
3	**10** (20)	23	**1a**+**3a**	4.7	n.d.[c]	1.43
4[a]	Ag_2CO_3 (10) **10** (20)	61	**1a**+**2a**	98.2	49	19.2
5[b]	**9c** (10)	53	**1a**+**2a**	90	68	27.0

[a]The mixture of Ag_2CO_3 and **10** was stirred for 1 h at rt before *rac*-**1a** was added. [b]Reaction time = 6 h. [c]n.d. = not determined.

carbonate cannot mediate the cyclization (entry 2). Interestingly, when a mixture of phosphoric acid **10** and silver carbonate in CH_2Cl_2 was stirred at room temperature for 1 h, the resulting catalyst system was found to be capable of catalyzing the kinetic resolution. The excellent enantioselectivity (98.2% ee) of the recovered starting material **1a** was achieved when the conversion was 61% (*s* = 19; entry 4). The selectivity was comparable to that for the experiment in which 10 mol % chiral silver phosphate **9c** was used (*s* = 27; entry 5). The considerably lower *s* factor indicated that other species (e.g., coexisting carbonate anions in the reaction system) may deteriorate the catalytic efficiency of **9c**.

Although there is a lack of conclusive evidence to establish the coordination mode of the silver−π-allene complex,[17] we tentatively propose an η^2-allene complex with silver on the basis of the structure and reactivity of other π-allene complexes of group-11 metals and related computational studies.[18] To interpret the excellent enantioselectivity achieved in our system, a quadrant diagram in which the shaded quadrants represent the hindered side (Scheme 2) can be used. When the racemic α-allenic alcohol approaches the metal center, the *R* enantiomer of **1** can preferentially coordinate the metal center while the *S* enantiomer remains in the reaction mixture, since the bulky R group in the former would preferentially lie in the unhindered area. The bonding *R* isomer subsequently undergoes cyclization to form a dihydrofuranylsilver species. After the subsequent protodemetalation and ligand exchange with the allenic alcohol, the corresponding enantiomerically enriched 2,5-dihydrofuran is formed to regenerate the catalytic species.

On the basis of the proposed model, the substituent at C(2) would certainly interact with the backbone of the quadrant. This was indeed the case when a methyl group was introduced at C(2), as shown in **1u** (Scheme 3A), for which *s* dramatically dropped to 2.8 with a sluggish reaction. For substrate **1t** bearing methyl and phenyl groups at C(1) (Scheme 3B), raising the reaction temperature to room temperature pushed the reaction

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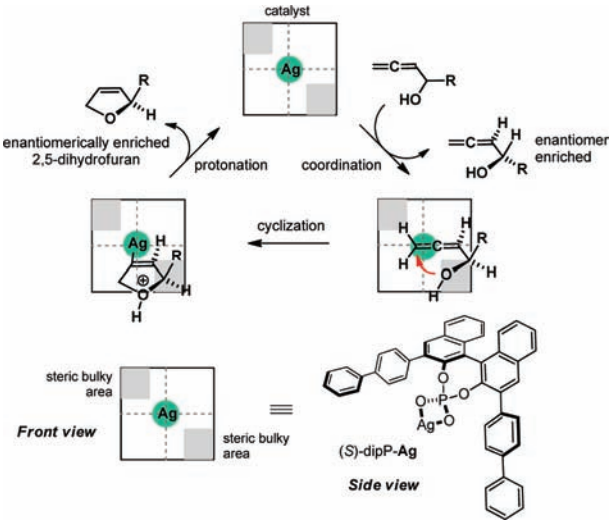
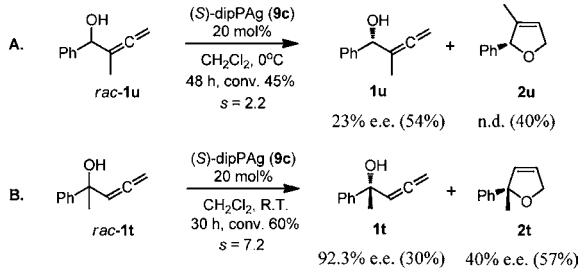
Scheme 2. Proposed Mechanism for Kinetic Resolution



Scheme 3. Sterically Bulky Substrates



to reach a high level of conversion (69%) and furnish excellent enantioselectivity of the recovered starting material (s = 7.2 and 92.3% ee for **1t**, vs s = 6.8 in Table 3) (see the SI for the determination of the absolute configuration). The bent distal C=C bond and the extra C(1)−C(2) σ bond allow the sterically bulky quaternary carbon center in **1t** to move away from the hindered quadrant region.

In summary, for the first time, an excellent level of enantioselectivity has been achieved in the kinetic resolution of α-allenic alcohols bearing a variety of functional groups through chiral silver phosphate-catalyzed cycloisomerization. The proposed mechanism shows that a silver−allene complex and the structure in the chiral phosphate are responsible for the success of high stereoselectivity. This efficient approach leading to both enantiomerically enriched α-allenic alcohols and 2,5-dihydrofurans opens an avenue for future method development and synthesis of biologically interesting natural products.[19] Further investigations of other silver-catalyzed enantioselective cycloisomerizations involving allenes in the context of natural product synthesis are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, synthetic applications, and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

rhong@sioc.ac.cn

Notes

The authors declare no competing financial interest.

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(19) The gram-scale syntheses of **1a** and **1s** and their synthetic applications are exemplified in the SI.