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Kinetic resolution of racemic tertiary allylic alcohols through S_N2' reaction using a chiral bisphosphoric acid/silver(I) salt co-catalyst system†

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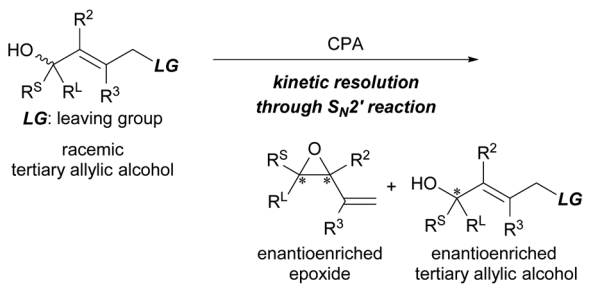
A highly efficient kinetic resolution (KR) of racemic tertiary allylic alcohols was achieved through an intramolecular allylic substitution reaction using a co-catalyst system composed of chiral bisphosphoric acid and silver carbonate. This reaction afforded enantioenriched diene monoepoxides along with the recovery of tertiary allylic alcohols in a highly enantioselective manner, realizing an extremely high *s*-factor in most cases. The present method provides a new access to enantioenriched tertiary allylic alcohols, multifunctional compounds that are applicable for further synthetic manipulations.

Introduction

Tertiary alcohols and their derivatives are present in a wide range of natural products and biologically active molecules. Synthetic methods for their preparation in an enantioenriched form, however, are challenging.[1] One of the most common approaches investigated thus far is the enantioselective nucleophilic addition to ketones using a chiral catalyst.[2] Another potential method is the catalytic kinetic resolution (KR)[3] of racemic tertiary alcohols. In contrast to the catalytic KR of racemic secondary alcohols,[4] reliable methods for the non-enzymatic KR of tertiary alcohols remain few.[5–9] Several groups have reported the use of chiral Lewis base (nucleophilic) catalysts[6] and chiral transition metal catalysts.[7] In the methodologies reported for the KR of racemic tertiary alcohols in recent years, chiral phosphoric acids (CPAs), which are one of the most powerful and privileged organocatalysts employed in a broad range of enantioselective transformations,[10] have proven to be excellent catalysts.[8] Several reaction systems, such as acetalization,[8a–c] transesterification,[8d] condensation,[8e] enamine/imine tautomerization,[8f] and S_N1-type reaction,[8g] have been established in a highly resolved manner using CPAs as the efficient chiral Brønsted acid catalyst.

With the aim of adding a new entry to catalytic KR using CPAs, we set out to develop a method for the KR of tertiary allylic alcohols,[9d] synthetically useful chiral building blocks. In order to establish a novel reaction system for the KR of racemic tertiary allylic alcohols, we envisioned a catalytic intramolecular S_N2' reaction using CPA,[11,12] *i.e.*, KR through the formation of enantioenriched epoxides (Scheme 1).[13] Considering the intramolecular S_N2' reaction, the relative position of the leaving group (***LG***) to the alcohol unit, namely, the oxygen nucleophile, is apparently defined by the geometry of the double bond. Hence, it was expected that the effective recognition of enantiomeric tertiary allylic alcohols would be realized by using a CPA catalyst despite the stereogenic centre having all non-hydrogen substituents.

Recently, we have developed an enantioselective intramolecular S_N2' reaction using a co-catalyst system composed of chiral bisphosphoric acid catalyst (*R*)-**1a**[12c,14] and arylboronic acid (or silver carbonate) as a weakly Lewis acidic additive (Scheme 2a).[12c] In the reported co-catalyst system, achiral tertiary allylic alcohols **2** having a normal ring structure (five- or six-membered ring) at the allylic position and trichloroacetimidate as the leaving group (***LG***) underwent an intramolecular S_N2' reaction smoothly, giving rise to



Scheme 1 KR of enantiomeric tertiary allylic alcohols through an intramolecular S_N2' reaction.

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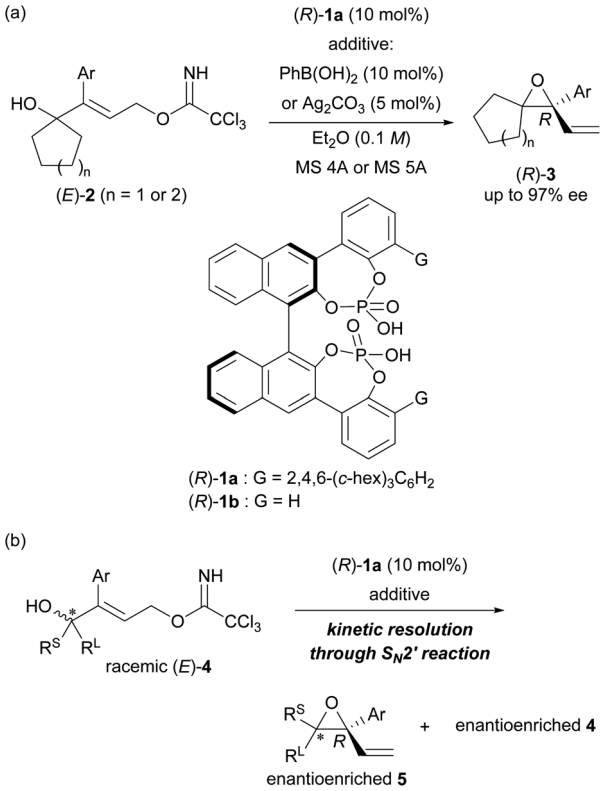


Scheme 2 (a) Enantioselective intramolecular S_N2' reaction catalysed by (*R*)-**1a** (previous work). (b) Catalytic KR of racemic tertiary alcohols through the intramolecular S_N2' reaction developed in the present study.

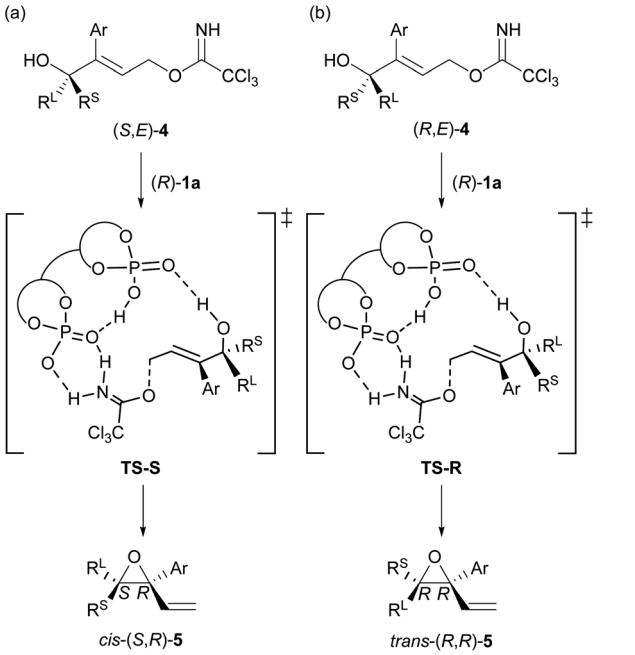


Fig. 1 Prediction of stereochemical outcomes in the present KR of racemic (*E*)-**4** through the intramolecular S_N2' reaction using the (*R*)-**1a**/additive co-catalyst system. The transition states in the absence of an additive are illustrated for clarity. (a) The reaction of (*S*,*E*)-**4**. (b) The reaction of (*R*,*E*)-**4**.

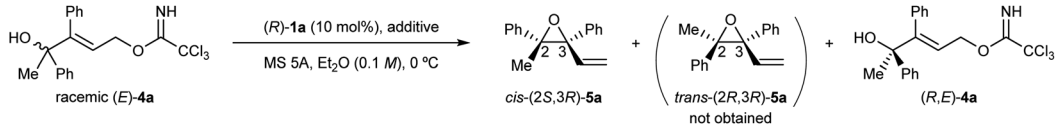
enantioenriched diene monoepoxides (*R*)-**3** as multifunctional products for further manipulation. In this enantioselective intramolecular S_N2' reaction, both arylboronic acid and silver carbonate were found to function as an efficient additive to suppress the catalyst deactivation process,§ and hence, to improve the yields of **3** markedly without compromising the enantioselectivities. We thus replaced the cyclic structure introduced at the allylic position with a tertiary stereogenic centre, resulting in racemic tertiary allylic alcohols (*E*)-**4** (Scheme 2b). Here we report the development of a highly efficient KR of racemic tertiary allylic alcohols (*E*)-**4** through the intramolecular S_N2' reaction using the co-catalyst system composed of chiral bisphosphoric acid (*R*)-**1a** and a weakly Lewis acidic additive.

Results and discussion

At the outset of our studies, we predicted the stereochemical outcome of the present KR through the intramolecular S_N2' reaction (Fig. 1) by considering the previous results in the epoxide formation reaction of (*E*)-**2** using the (*R*)-**1a**/additive co-catalyst system (Scheme 2a). We anticipated that the newly generated stereogenic centre at the allylic position of formed epoxide **5** should be (*R*)-stereochemistry in the present KR of (*E*)-**4**. Hence, the reaction of racemic (*E*)-**4** under the influence of the (*R*)-**1a**/additive co-catalyst system would afford the diastereomers of *trans*-(*R*,*R*)-**5** and *cis*-(*S*,*R*)-**5** formed from (*R*,*E*)-**4** and (*S*,*E*)-**4**, respectively (Fig. 1). Meanwhile, previous mechanistic studies on the enantioselective reaction of (*E*)-**2** revealed that epoxide (*R*)-**3** was formed in an *anti*-S_N2' fashion,[12a,c]¶ in which the leaving group and the oxygen nucleophile were oriented in an *anti*-relationship with respect to each other. On the basis of the *anti*-S_N2' pathway, the present intramolecular S_N2' reaction would proceed *via* transition states, **TS-S** and **TS-R**,‖ depicted in Fig. 1. In these transition states, if chiral bisphosphoric acid (*R*)-**1a** would effectively distinguish the chirality at the allylic position, it was assumed that one of diastereomeric *cis*- and *trans*-epoxides **5** would form predominantly.

With the above prediction in mind, we commenced the intramolecular S_N2' reaction of racemic tertiary allylic alcohol (*E*)-**4a** using the (*R*)-**1a**/additive co-catalyst system for KR. We confirmed the validity of the previous reaction conditions[12c] using optimized chiral bisphosphoric acid (*R*)-**1a** and the additive, *i.e.*, phenylboronic acid or silver carbonate, in the presence of molecular sieves (MS) 5A in diethyl ether at 0 °C. As shown in Table 1, the co-catalyst system was applicable to the intramolecular S_N2' reaction of tertiary allylic alcohol (*E*)-**4a**, and KR was achieved as intended with a high *s*-factor,[15] regardless of the presence or absence of the additive (entries 1–3). Although phenylboronic acid functioned well as an additive in the previous intramolecular S_N2' reaction of (*E*)-**2**,[12c] the use of silver carbonate in the present KR resulted in a better material balance (entry 2 *vs.* 1), albeit with a slightly reduced *s*-factor. The absolute stereochemistry of recovered (*E*)-**4a** was

Table 1 KR of racemic tertiary allylic alcohol (*E*)-**4a** through intramolecular S_N2' reaction using (*R*)-**1a**/additive co-catalyst system[a]



Entry	Additive	Time (h)	Yield[b] of **5a**/**4a** (%)	Calculated conversion c [c] (%)	dr[d] of **5a** *cis*/*trans*	ee[e] of **5a**/**4a** (%)	*s*-Factor[f]
1	$PhB(OH)_2$ (10 mol%)	96	35/30	48.9	>98 : <2	98/94	351
2	Ag_2CO_3 (5 mol%)	80	46/52	47.3	>98 : <2	98/88	290
3	None	96	33/25	47.8	>98 : <2	98/90	305

[a] Unless otherwise noted, all reactions were carried out using 10 mol% of (*R*)-**1a**, 0.1 mmol of racemic (*E*)-**4a**, and MS 5A (40 mg) in Et_2O (1.0 mL) at 0 °C. [b] The yield of **5a** is indicated, as determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c] Conversion c was calculated from $ee_{product}$ of *cis*-**5a** and $ee_{recovered}$ of recovered (*E*)-**4a**: $c = ee_{recovered}/(ee_{product} + ee_{recovered})$. [d] The diastereomeric ratio (dr) of **5a** was determined by ^1H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase column. [f] *s*-Factor was calculated from the calculated conversion c and $ee_{product}$ of *cis*-**5a**: $s = \ln[(1 - c)(1 - ee_{product})]/\ln[(1 - c)(1 + ee_{product})]$.

determined to be *R*-isomer through derivatization into a stereochemically known compound.[16] Since the efficient KR was achieved with the recovery of (*R*,*E*)-**4a** in a highly enantioselective manner, the substitution product, diene monoepoxide **5a**, was formed as a single diastereomer with a *cis*-relative configuration and the 2*S*,3*R* absolute stereochemistry,** as predicted in Fig. 1. These results strongly suggest that the conformation at the stereogenic centre of the tertiary alcohol is strictly recognized by catalyst (*R*)-**1a**, in particular, with respect to substituent G introduced at the *ortho*-positions of the phenyl rings (*vide infra*). This is presumably because the transition states of the *anti*-S_N2' reaction pathway are well stabilized by catalyst (*R*)-**1a** through multiple interactions involving hydrogen bonds,¶ and hence, the relative position of the leaving group as well as the nucleophilic oxygen is firmly defined by the catalyst.

With the suitable co-catalyst system composed of (*R*)-**1a** (10 mol%) and silver carbonate (5 mol%) in hand (Table 1, entry 2), we next investigated the generality of the present KR using a series of tertiary allylic alcohols (*E*)-**4** having different electronic and steric properties. As shown in Table 2, high *s*-factors were achieved in most cases, whereas marked electronic and steric effects were observed in specific cases. A variety of R^L substituents could be introduced at the stereogenic centre (entries 1–8), and efficient KR was achieved with (*E*)-**4** having the aryl moiety as an R^L substituent and methyl group as an R^S substituent, except when the substrate had an electronically enriched aryl ring, *i.e.*, the 4-methoxyphenyl group, as an R^L substituent (entry 4). In this case, the vinylogous Wagner–Meerwein shift predominated over the desired intramolecular S_N2' reaction, affording **6e** as a racemic mixture in 48% yield. The present KR was also applicable to substrate **4j**, which had aliphatic substituents (R^L = *i*Pr, R^S = Me) at the stereogenic centre (entry 9), leading to the formation of enantioenriched **5j** with a relatively high *s*-factor. More interestingly, the high *s*-factor was substantially maintained even when the methyl group was replaced by the ethyl group as an R^S substituent, which increased the steric demand (entry 10); efficient recognition was attained between the phenyl and ethyl groups. Further investigation was conducted by changing the Ar group at the carbon–carbon double bond (entries 11–19). Although high *s*-factors were achieved in most cases, some Ar substituents exerted marked electronic and steric effects (entries 14 and 17), presumably because having unfavourable Ar substituents destabilizes a positively charged transient species generated during the course of the intermolecular S_N2' reaction. In fact, an electron-withdrawing substituent, namely, the trifluoromethyl group, introduced at the *para*-position of the phenyl ring suppressed the S_N2' reaction completely, resulting in no product formation (entry 14). The sterically congested *ortho*-substituted aryl ring also impeded the intended reaction (entry 17). Meanwhile, the heteroaryl substituent could be introduced at the double bond, however the substrate having the thiophenyl group, (*Z*)-**4t**,†† underwent the S_N2' reaction to afford a diastereomeric mixture of *cis*- and *trans*-**5t** (80 : 20) with fairly good enantioselectivities for both diastereomers (entry 19). In addition, even though an almost half conversion of (*Z*)-**4t** (c = 48.5), moderate enantioselectivity was observed in recovered (*Z*)-**4t**. These results suggest that both enantiomers of (*S*,*Z*)- and (*R*,*Z*)-**4t** were consumed in parallel to some extent, affording *cis*-(2*S*,3*S*)-**5t** and *trans*-(2*R*,3*S*)-**5t**, respectively.‡‡ Consequently, the KR of (*S*,*Z*)- and (*R*,*Z*)-**4t** did not take place efficiently, although both diastereomers **5t** were obtained in an enantioenriched form.

The efficiency of the developed KR was further demonstrated by scaling up the reaction (Scheme 3). Racemic (*E*)-**4a** (0.40 g, 1.0 mmol) underwent the intramolecular S_N2' reaction under the optimized reaction conditions while maintaining the high *s*-factor. *Cis*-(2*S*,3*R*)-**5a** was formed as the single diastereomer along with the recovery of (*R*,*E*)-**4a** in a highly enantioselective manner. As readily expected, formed epoxide **5a** was easily separable from recovered tertiary alcohol **4a** by silica-gel column chromatography.

In addition, simple derivatization of enantioenriched epoxide *cis*-(2*S*,3*R*)-**5a** and recovered tertiary alcohol (*R*,*E*)-**4a** was also carried out (Scheme 4). Treatment of the enantioenriched epoxide product *cis*-(2*S*,3*R*)-**5a** under acidic conditions using water as the nucleophile afforded corresponding allylic

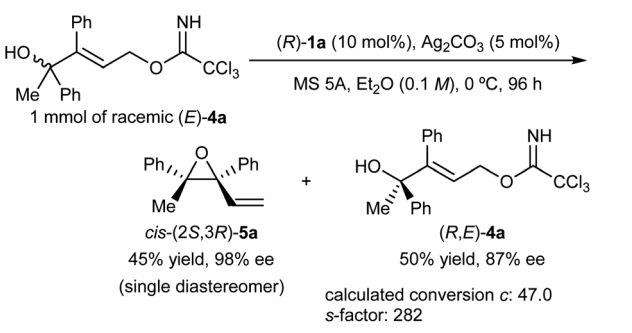
Table 2 KR of racemic tertiary allylic alcohol (*E*)-**4a** through intramolecular S_N2' reaction using (*R*)-**1a**/silver carbonate co-catalyst system[a]

Entry	4	R^L	R^S	Ar	Yield[b] of 5/4 (%)	Calculated conversion c[c] (%)	dr[d] of 5	ee[e] of 5/4 (%)	*s*-Factor[f]
1	**4b**	4-$CF_3C_6H_4$	Me	Ph	34/47	46.3	>98 : <2	94/81	81
2	**4c**	4-ClC_6H_4	Me	Ph	43/45	49.5	>98 : <2	94/92	107
3	**4d**	4-MeC_6H_4	Me	Ph	40/40	47.5	>98 : <2	94/85	88
4	**4e**	4-$MeOC_6H_4$	Me	Ph	—[g]/11	—	>98 : <2	—/67	—
5	**4f**	3-ClC_6H_4	Me	Ph	40/45	47.2	>98 : <2	95/85	106
6	**4g**	3-MeC_6H_4	Me	Ph	41/43	45.3	>98 : <2	94/78	76
7	**4h**	3-$MeOC_6H_4$	Me	Ph	45/37	51.0	>98 : <2	90/94	67
8[h]	**4i**	2-ClC_6H_4	Me	Ph	37/49[i]	37.3	>98 : <2	94/56	57
9	**4j**	*i*Pr	Me	Ph	32/52	35.3	>98 : <2	92/50	40
10	**4k**	Ph	Et	Ph	49/39	50.7	>98 : <2	95/98	174
11[j]	**4l**	Ph	Me	4-$MeOC_6H_4$	44/36	49.4	>98 : <2	86/84	35
12	**4m**	Ph	Me	4-ClC_6H_4	34/49	37.8	>98 : <2	92/56	42
13	**4n**	Ph	Me	4-PhC_6H_4	26/71	27.5	>98 : <2	95/36	56
14	**4o**	Ph	Me	4-$CF_3C_6H_4$	ND[k]	—	—	—	—
15	**4p**	Ph	Me	3-MeC_6H_4	30/63	36.8	>98 : <2	96/56	86
16	**4q**	Ph	Me	3-ClC_6H_4	30/51	32.6	>98 : <2	97/47	105
17	**4r**	Ph	Me	2-MeC_6H_4	ND[k]	—	—	—	—
18	**4s**	Ph	Me	2-Naphthyl	53/34	54.2	>98 : <2	84/99.5	65
19[l]	**4t**	Ph	Me	2-Thiophenyl	40/49[m]	48.5[n]	80 : 20[n]	86, 90[n]/48	—[o]

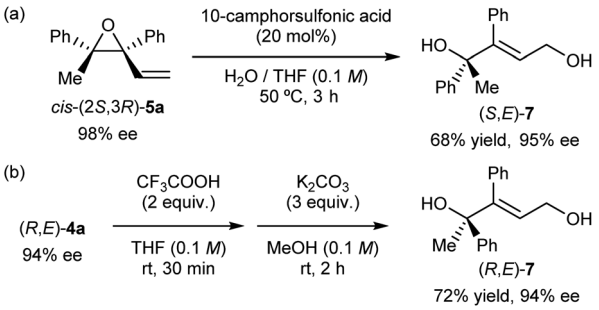
[a] Unless otherwise noted, all reactions were carried out using 10 mol% of (*R*)-**1a**, 5 mol% of Ag_2CO_3, 0.1 mmol of racemic (*E*)-**4**, and MS 5A (40 mg) in Et_2O (1.0 mL) at 0 °C. [b] The yield of **5**, as determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as the internal standard, is indicated. [c] Conversion c was calculated from $ee_{product}$ of *cis*-**5** and $ee_{recovered}$ of recovered (*E*)-**4**: $c = ee_{recovered}/(ee_{product} + ee_{recovered})$. [d] The diastereomeric ratio (dr) of **5** was determined by ^1H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase column. [f] *s*-Factor was calculated from the calculated conversion c and the $ee_{product}$ of *cis*-**5**: $s = \ln[(1-c)(1-ee_{product})]/\ln[(1-c)(1+ee_{product})]$. [g] **6e** was formed as a major product (48% yield) in a racemic form along with a small amount of desired **5e** as a mixture of other unknown byproducts. [h] At −40 °C for 20 h. [i] (*S*,*E*)-**4i** was recovered due to the nomenclature of the substituent priority. [j] At −40 °C for 72 h. [k] ND: desired product **5** was not detected even at room temperature for 72 h. [l] At −40 °C for 120 h. [m] (*R*,*Z*)-**4t** was recovered due to the nomenclature of the substituent priority. [n] *Cis*-(2*S*,3*S*)-**5t** was formed as the major diastereomer with 86% ee along with *trans*-(2*R*,3*S*)-**5t** as a minor product with 90% ee. Therefore, conversion c was calculated from 51% ee for $ee_{product}$ averaged at the 2-position of *cis*- and *trans*-**5t**. See ESI for details. [o] *s*-Factor could not be calculated because *trans*-(2*R*,3*S*)-**5t** was formed from (*R*,*Z*)-**4t** as the minor diastereomer in this case.

alcohol (*S*,*E*)-**7** in acceptable yield (Scheme 4a). In the present S_N2' ring-opening reaction of the epoxide, the (*E*)-geometrical isomer of **7** was formed exclusively without marked loss of enantiomeric purity. Enantioenriched (*R*,*E*)-**4a** thus recovered was converted into (*R*,*E*)-**7** in 72% yield without any loss of enantiomeric purity through the two-step transformation (Scheme 4b), *i.e.*, the S_N2 reaction of (*R*,*E*)-**4a** with trifluoroacetic acid, followed by the transesterification of the formed mono-trifluoroacetate of (*R*,*E*)-**7** using methanol.

As the developed KR through the intramolecular S_N2' reaction of racemic tertiary allylic alcohols (*E*)-**4** was demonstrated



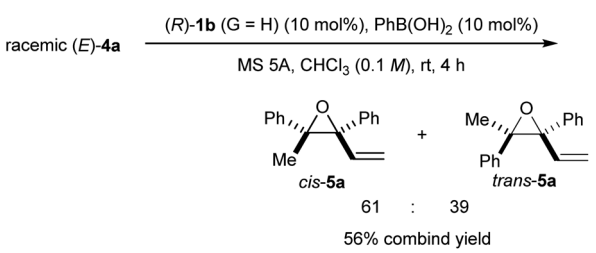
Scheme 3 Large-scale experiment to demonstrate the utility of the present KR.



Scheme 4 (a) Derivatization of enantioenriched epoxide *cis*-(2*S*,3*R*)-**5a** into allylic alcohol (*S*,*E*)-**7**. (b) Hydrolysis of enantioenriched (*R*,*E*)-**4a** into allylic alcohol (*R*,*E*)-**7**.

to be highly efficient, our interest then turned to the origin of the high efficiency of the present KR and the stereochemical outcome. In order to gain a mechanistic insight of the present efficient KR, we carried out a reaction of racemic (*E*)-**4a** under the influence of (*R*)-**1b** (G = H) having no substituents at the *ortho*-positions of the phenyl rings (Scheme 5). The reaction was performed in chloroform using $PhB(OH)_2$ as an additive given the low solubility of (*R*)-**1b**/silver carbonate co-catalyst in diethyl ether.§§ A mixture of *cis*- and *trans*-**5a** was formed with a slight excess of *cis*-**5a**. This result clearly suggests that the sterically bulky substituent (G = 2,4,6-(*c*-hex)$_3$C$_6$H$_2$) of catalyst (*R*)-**1a** is key not only to controlling the newly generated stereogenic centre at the allylic position but also to recognizing the configuration of the racemic stereogenic centre.

As shown in Fig. 2, this remarkable substituent effect is readily anticipated from the 3D structures of the transition states, **TS-S$_{model}$** and **TS-R$_{model}$**, using the model system composed of substrate (*E*)-**4a** and simplified catalyst (*R*)-**1b** (G = H). These transition states were optimized by DFT calculation,[17–19]‖ in accordance with the *anti*-S_N2' reaction pathway.¶ Before considering the substituent effect of the catalyst, we summarize the intriguing features of these transition states, as follows: Two phosphoric acid units interact with each other through a hydrogen bond.[14] These two phosphoric acid units have specific roles and their involvement in the bond recombination sequence is essential. One phosphoric acid forms a hydrogen bond between the phosphoryl oxygen P=O and the hydroxy proton of the tertiary alcohol. This hydrogen bond is considered to promote the nucleophilic attack of the alcohol oxygen on the double bond, although the present intramolecular S_N2' reaction proceeds through a stepwise pathway and these transition states indicate the first C–O bond cleavage step of the leaving group. The nucleophilic attack of the alcohol oxygen follows the C–O bond cleavage and is involved in the subsequent epoxide formation step. In contrast, the acidic OH of the other phosphoric acid protonates the nitrogen of the trichloroacetimidate moiety to activate the leaving group. Furthermore, the phosphoryl oxygen interacts with the N–H proton of the imidate moiety and hence, the double hydrogen bonding interaction occurs between this phosphoric acid unit and the trichloroacetimidate moiety. These multiple hydrogen bonds stabilize the transition states and determine the relative position between catalyst (*R*)-**1b** and substrate (*E*)-**4a**. In other words, the unique features of these model transition states



Scheme 5 Intramolecular S_N2' reaction of racemic (*E*)-**4a** using the co-catalyst system of (*R*)-**1b** (G = H) and $PhB(OH)_2$ in chloroform.

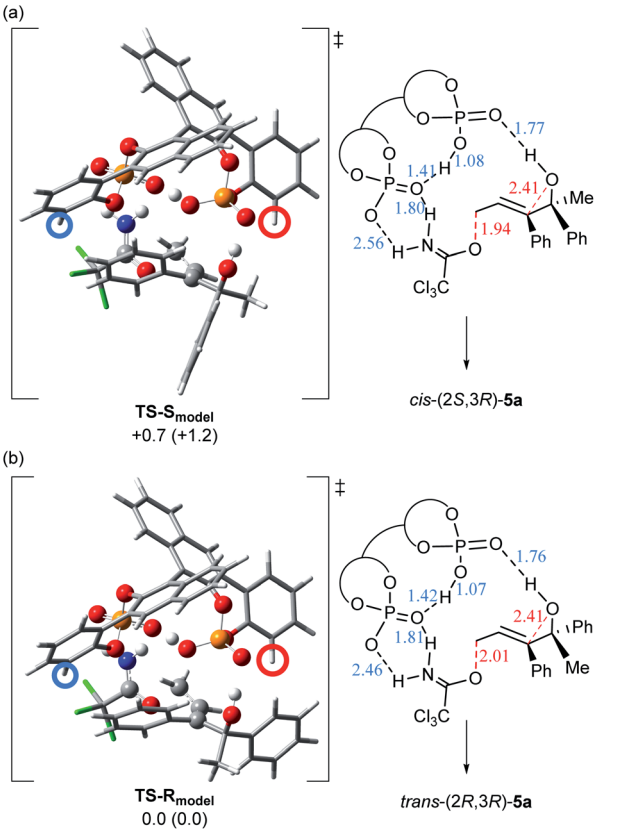


Fig. 2 3D structures and schematic representation models of the most energetically favourable transition states for the C–O bond cleavage step, **TS-S$_{model}$** and **TS-R$_{model}$**. The 3D structures of the fragments are represented as follows: phosphoric acid units and atoms involved in the bond recombination sequence and the hydrogen bonding interaction: "ball and bond type" model; and the other atoms, such as bisphosphoric acid backbone and substrate: "tube" model. The *ortho*-position of the phenyl ring is indicated by circles, where the substituent is introduced in the actual catalytic system. Relative free energies (kcal mol^{-1}) of the optimized structures at the B97D/6-31G(d) level[18] in the gas phase are shown in parentheses. Relative free energies (kcal mol^{-1}) obtained by single-point energy calculations at the same level are shown for the optimized transition states in the solution phase according to the SCRF method based on CPCM (ether).[19] Hydrogen bond lengths are indicated in blue (angstroms) and cleaved and formed C–O bond lengths are indicated in red (angstroms): (a) **TS-S$_{model}$** generated from (*R*)-**1b** (G = H) and (*S*,*E*)-**4a**. (b) **TS-R$_{model}$** generated from (*R*)-**1b** (G = H) and (*R*,*E*)-**4a**.

strongly suggest that chiral bisphosphoric acid catalyst plays a crucial role in the smooth acceleration of the present intramolecular S_N2' reaction. However, unlike the experimental result shown in Scheme 5 where the formation of *cis*-(2*S*,3*R*)-**5a** slightly dominated, **TS-R$_{model}$** (Fig. 2b), affording *trans*-(2*R*,3*R*)-**5a**, is energetically favorable, although the energy difference is not significant in the solution phase ($\Delta\Delta G^{\neq}$ = 0.7 kcal mol^{-1}) ¶¶.

Further consideration of the real catalytic system was continued on the basis of these unique model transition states (Fig. 2). When a sterically bulky substituent (G = 2,4,6-(*c*-hex)$_3$C$_6$H$_2$) is introduced at the *ortho*-position of the phenyl ring (indicated by circles in the 3D structures) of (*R*)-**1b**, giving (*R*)-**1a**,

in **TS-R$_{model}$** generated from (*R*,*E*)-**4a** (Fig. 2b), it is readily assumed that a large steric repulsion occurs between the bulky substituent (the position indicated by the red circle) and the phenyl group attached to the stereogenic centre. Therefore, the formation of *trans*-(2*R*,3*R*)-**5a** from (*R*,*E*)-**4a** is efficiently suppressed. On the other hand, in the case of **TS-S$_{model}$** generated from (*S*,*E*)-**4a** (Fig. 2a), the transition state structure is maintained without steric congestion because the sterically less hindered methyl group faces the substituent side (the position indicated by the red circle) of catalyst (*R*)-**1a**. Therefore, *cis*-(2*S*,3*R*)-**5a** is formed exclusively.

Conclusion

A highly efficient KR of racemic tertiary allylic alcohols was developed through the intramolecular S_N2' reaction using the chiral bisphosphoric acid/silver carbonate co-catalyst system. In the established KR system, *cis*-epoxides were formed in a highly diastereo- and enantio-selective manner along with the recovery of tertiary allylic alcohols with high enantioselectivity, achieving a markedly high *s*-factor in most cases. Our protocol, namely, the intramolecular allylic substitution reaction catalysed by CPAs, provides a new entry to the catalytic KR of tertiary alcohols, which have been employed as synthetically useful chiral building blocks, in a highly enantioselective manner. Further elucidation of the mechanism of the present KR and application of the allylic substitution reaction to the enantioselective construction of the tetrasubstituted stereogenic centre is underway in our laboratory.

Data availability

The exploratory investigation, experimental procedures, computational data, and characterization data are available.

Author contributions

S. K.: conceptualization, data curation, formal analysis, and investigation (experimental studies). J. K.: data curation, formal analysis, and investigation (theoretical and experimental studies). N. S.: data curation, formal analysis, and investigation (mechanistic studies). S. U.: data curation, formal analysis, and investigation (mechanistic studies and derivatization). M. T.: conceptualization, project administration, writing – review & editing, supervision, and funding acquisition.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

§ The formation of the corresponding phosphate ester through the S_N2 reaction of substrate **2** with bisphosphoric acid **1a** at the allylic position is responsible for the catalyst deactivation. These additives, arylboronic acid and silver carbonate, efficiently suppress the undesirable S_N2 reaction to avoid the catalyst deactivation.

¶ In the presence of the additive (either phenylboronic acid or silver carbonate), it has been confirmed that the reaction of **2** (Ar = Ph) proceeds in an *anti*-S_N2' fashion under the influence of catalyst (*R*)-**1a**. See ESI for details.

‖ As shown in Table 1, the presence or absence of additives has a notable influence on the yield but a minimal effect on both the stereochemical outcome and the efficiency of the KR. Hence, these schematic transition states were able to draw in the absence of additives, likewise transition states of the model systems were calculated without using additives.

** On the basis of the absolute stereochemistry of recovered (*R*,*E*)-**4a**, the absolute stereochemistry at the 2-position of epoxide **5a** was predicted to be 2*S*. On the other hand, the relative stereochemistry of epoxide **5** was assigned to be *cis*-isomer by the NOE experiment of **5l** under the NMR measurement. Consequently, the combination of these stereochemical assignments resulted in the formation of *cis*-(2*S*,3*R*)-**5a** as the major product. See ESI for details.

†† Although the geometry of **4t** is nomenclated to be *Z* due to the priority of the substituents, the relative location of the substituents attached to the C=C double bond of (*Z*)-**4t** is the same as that of other substrates (*E*)-**4**.

‡‡ The absolute stereochemistry of *trans*-**5t** was assigned as (2*R*,3*S*), which was derived from (*R*,*Z*)-**4t**, on the basis of the distribution of the stereochemical outcomes of *cis*- and *trans*-**5t** and recovered (*Z*)-**4t**. See ESI for details.

§§ The reaction of (*E*)-**4a** using the co-catalyst system of (*R*)-**1a** (G = 2,4,6-(*c*-hex)$_3$C$_6$H$_2$) and PhB(OH)$_2$ in chloroform at room temperature for 4 h afforded *cis*-(2*S*,3*R*)-**5a** (12% yield) as the single diastereomer along with the formation of a significant amount of the vinylogous Wagner–Meerwein shift product, ketone **6a** (51% yield). See ESI for details.

¶¶ A(1,2) strain, which causes steric congestion between the phenyl groups introduced at the stereogenic centre and the double bond in **TS-S$_{model}$**, might be responsible for the calculated energy gap.

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