Molecular Transformation Based on an Innovative Catalytic System

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Novel innovative catalytic systems such as hydrogen-bond donors and thiourea hybrid catalysts have been developed for the asymmetric synthesis of biologically important pharmaceuticals and natural products. Benzothiadiazines possess a stronger hydrogen-bond donor ability compared to thioureas and exhibit remarkable catalytic performance for the activation of \( \alpha,\beta \)-unsaturated amides. Hybrid thioureas (bearing an arylboronic acid and an ammonium salt) efficiently promote the hetero-Michael addition to \( \alpha,\beta \)-unsaturated carboxylic acids and the \( O \)-alkylation of keto enols with 5-chlorofuran-2(5\( H \))-one. These hybrid catalysts enable the first total synthesis of non-racemic avenaol, a noncanonical strigolactone, as well as the asymmetric synthesis of several pharmaceuticals. In addition, this study discovers unique chemical phenomena (i.e., the dual role of benzoic acid as a boron ligand and a proton shuttle, the chirality switch of products by solvent used, and the dynamic kinetic resolution of a racemic electrophile in an \( S_N 2 \)-type reaction).

Key words catalysis; chirality switch; thiourea; arylboronic acid; ammonium salt; avenaol

1. Introduction

A catalyst is a central component in accelerating a chemical reaction by lowering the energy barrier of a transition state but is not consumed during the reaction. Therefore, a chemically unchanged catalyst can be recovered at the end of a reaction. Catalyzed reactions generally occur under mild reaction conditions and a broader substrate scope. One type of catalyst is an enzyme. Various enzymes promote important biochemical reactions in humans and other living creatures. Complex life would be impossible without these enzymes as they allow specific molecules to come together and provide the necessary products when required. Synthetic chemistry also requires a variety of catalysts to accomplish a wide range of reactions for supplying requisite chemicals, drugs, and materials. From a green chemistry viewpoint, reactions should be carried out using abundant, non-toxic substrates (without any protecting groups) at room temperature under neutral conditions. These requirements can be achieved using well-designed artificial catalysts. Therefore, this study develops chiral multifunctional hydrogen-bond (HB) donor catalysts for the asymmetric synthesis of biologically active molecules. This article includes research of three different types of organocatalysts and their synthetic applications: (1) benzothiadiazine-type HB donors, (2) aminothiourea–arylboronic acid hybrid catalysts, and (3) quaternary ammonium salts with a thiourea moiety.

2. Asymmetric Reactions Using Bifunctional Cyclic Guanidine Catalysts

2.1. Design of Bifunctional Cyclic Guanidines

HB donors are important and effective catalysts in organocatalysis. Thiourea is a representative motif due to the suitable positioning of two N–H protons on the molecule (i.e., the distance between these protons and the dihedral angle of N–C–N are 2.1 Å and 114°, respectively). We have already developed bifunctional aminothiourea \( 1a \), in which both the thiourea moiety and the tertiary amine cooperatively activate a nucleophile and an electrophile, respectively. The authors have also demonstrated that a wide range of asymmetric reactions (including the Michael addition, the Mannich reaction, the aza-Henry reaction, and the Neber reaction) are promoted by this catalyst to give corresponding products with high enantioselectivity.\(^1\)\(^2\) However, catalytic methods that use less active Michael acceptors, such as esters and amides, are still limited. In addition, \( 1a \) has a serious disadvantage; the catalyst decomposes when subjected to some kinds of oxidants and electrophiles due to the high reactivity of the sulfur atom.\(^2\)

Therefore, new HB donors bearing cyclic guanidine motifs were designed, in which the HB moiety and the aryl ring were linked by an electron-withdrawing group, as shown in Fig. 1.\(^3\) Furthermore, the acidities of the two N–H protons on the guanidine catalyst are enhanced by choosing a suitable tether (C=O or SO\(_2\)) as well as a substituent (R = F, CF\(_3\), etc.) on the benzene ring.

From a synthetic point of view, quinazoline-type and benzothiadiazine-type catalysts \( 2 \) and \( 3 \) were selected. Since guanidine catalysts that possess strong electron-withdrawing...
groups such as C=O and SO$_2$ are no longer expected to function as Brønsted bases, the tertiary amino group is essential for catalyzing reactions in the same manner as the bifunctional thiourea. These catalysts are readily synthesized in four steps from the corresponding anilines and anthranilic acids as is shown in Chart 1. To evaluate the HB-donating abilities of catalysts 1–3, their association constants ($K_1$) were determined by the titration of nBu$_4$NCl to a solution of each HB donor in acetonitrile. Consequently, the $K_1$ (M$^{-1}$) of 1a, 2a, and 3a were estimated as $1.2 \times 10^3$ ($\pm 37$), $4.9 \times 10^2$ ($\pm 18$), and $1.9 \times 10^3$ ($\pm 44$), respectively. The relative abilities of these HB donors are remarkably different and followed the order $3a > 1a > 2a$.

The most promising HB donor (3a) efficiently accelerated the isomerization of alkynoates to allenoates 3,4) and the epoxidation of $\alpha$, $\beta$-unsaturated amides 5) in a highly enantioselective manner.6)

2.2. The Intramolecular Oxa-Michael Addition of Hydroxylamine Derivatives

The $\alpha$, $\beta$-unsaturated amide 4a bears a hydroxylamine moiety and was selected as a substrate for the screening of catalysts for the asymmetric intramolecular oxa-Michael addition (AIOM, Table 1).7) Since N-benzyloxycarbonyl (Cbz)-hydroxylamine is a strong nucleophile and an active leaving group, the use of a strong base for the activation of the nucleophile may result in low enantioselectivity due to racemization via retro-Michael addition. Therefore, improving their HB-donating ability is a forceful strategy to facilitate the AIOM using poorly reactive Michael acceptors instead of increasing the basicity of the catalysts. Although the reaction of 4a did not efficiently proceed with conventional organic bases such as triethylamine and cinchonidine 6, bifunctional thiourea 1a and squaramide 7 moderately enhanced the cyclization of 4a to afford isoxazolidine 5a in acceptable enantioselectivities. However, long reaction times (four or five days) were needed to complete the reaction (entries 1–3). As was expected, the new guanidine-type catalysts 2a and 3a exhibited distinct catalytic activities. Both the chemical yield and the enantioselectivity were influenced in relation to the HB-donating ability (entries 4–6). In sharp con-

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**Fig. 1. Design of Bifunctional Guanidine Catalysts**

**Chart 1. Preparation of Bifunctional Quinazolines 2a–e and Benzothiadiazines 3a–f**

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**Biography**

Yoshiji Takemoto was born in 1960 in Osaka (Japan) and currently serves as a Professor in the Graduate School of Pharmaceutical Sciences at Kyoto University (Japan). He received his BSc (1983) and Ph.D. degrees (1988) from Osaka University under the supervision of Chuzo Iwata. Subsequently, he worked as a postdoctoral fellow with Prof. R. A. Holton at Florida State University (U.S.A.; 1988–1989) and with Dr. S. Terashima at the Sagami Chemical Research Center (Japan; 1989–1990). In 1990, he joined the Faculty of Pharmaceutical Sciences at Osaka University (Japan) as an Assistant Professor. In 1998, he moved as an Associate Professor to the Graduate School of Pharmaceutical Sciences at Kyoto University, where he was promoted to Professor in 2000. His research interests are focused on synthetic organic chemistry, transition-metal chemistry, organocatalysis, and the total synthesis of natural products.
trast to benzimidazole 8⁹,¹⁰ and quinazoline 2a, the reaction with benzothiadiazine 3a was completed within 24 h, giving a 92% yield of the desired product 5a with 95% enantiomeric excess (ee). Additional experiments with a series of fluorine-containing benzothiadiazine catalysts 3b–d revealed that 3c resulted in the best enantioselectivity (entries 7–9).

The catalyst 3a was applied to a variety of tertiary and secondary amides 4b–f, and the desired cyclized adducts 5b–f were obtained in the range of a 70–99% yield (Table 2). The enantioselectivities were somewhat affected by the substituents (R² and R³) of the amide moiety; more than 90% ee was achieved in the cases of the N-methylanilides

| Entry | Catalyst | Time (h) | Yield (%) | Ee (%) |
|-------|----------|----------|-----------|--------|
| 1     | 1a       | 120      | 88        | 81     |
| 2     | 6        | 24       | Trace     | n.d.   |
| 3     | 7        | 96       | 88        | 88     |
| 4     | 8        | 24       | Trace     | n.d.   |
| 5     | 2a       | 336      | 74        | 51     |
| 6     | 3a       | 24       | 92        | 95     |
| 7     | 3b       | 24       | 99        | 93     |
| 8     | 3c       | 24       | 99        | 97     |
| 9     | 3d       | 24       | 99        | 79     |

a) Isolated product. b) The ee values were determined by chiral HPLC analysis. c) n.d. = not determined.

| Entry | Product | Conditions | Yield (%) | Ee (%) |
|-------|---------|------------|-----------|--------|
| 1     | 5b      | rt, 24 h   | 89        | 92     |
| 2     | 5c      | rt, 24 h   | 97        | 84     |
| 3     | 5d      | rt, 24 h   | 99        | 96     |
| 4     | 5e      | 40 °C, 24 h| 99        | 90     |
| 5     | 5f      | 40 °C, 72 h| 70        | 84     |

a) Isolated yield. b) Determined by chiral HPLC analysis.
and benzylamides. In addition to their biological importance, the isoxazolidines 5 are regarded as β-hydroxy-δ-amino acid equivalents, following the cleavage of the N–O bond.

2.3. Synthetic Applications of the Oxa-Michael Addition

To highlight the synthetic utility of 5, a concise formal total synthesis of atorvastatin was performed from the Michael adduct 5e (Chart 2). The amide 5e was converted into a known synthetic intermediate 911 of atorvastatin by a three-step sequence consisting of amide–ester conversion, N–O bond cleavage, and cross-Claisen condensation with tert-butyl acetate.

The advantage of using the current AIOM of phenolic α,β-unsaturated amides is demonstrated by the first enantioselective synthesis of atorvastatin. The AIOM of the α,β-unsaturated ester 10 proceeded at an unprecedented low temperature (−20°C), providing the desired product 11. Next, double debenzylation and selective acetylation gave the target molecule in a 73% overall yield with a 94% ee.

An alternative example of AIOM is the first catalytic asymmetric synthesis of beraprost, which is used as a stable prostacyclin (PGI2) analogue.12 The formal total synthesis was achieved through the AIOM of the α,β-unsaturated Weinreb amide 12 into the optically active dihydrobenzofuran 13. The key steps were Rh-catalyzed C–H insertion, ketone reduction, and elongation of the C4 unit.

3. Asymmetric Reactions Using Amino Thiourea–Arylboronic Acid Hybrid Catalysts

3.1. Design of the Amino Thiourea–Arylboronic Acid Hybrid Catalysts

Complicated in their Michael addition applications, α,β-unsaturated carboxylic acids 15 are less electrophilic and possess acidic protons that could deactivate nucleophiles and catalysts. Therefore, an amino thiourea–arylboronic acid (ATBA) hybrid catalyst was designed according to the reaction mechanism mediated by ammonia lyase and aminomutase, because the aza-Michael addition to 15 has only been achieved with perfect selectivity by enzymes13 (Fig. 2). In enzymatic reactions, a carboxylate anion is stabilized by several HB interactions with arginine 299 and asparagine 340. It was expected that appropriate functional groups (such as thioureas, tertiary amines, and boronic acid) would function as HB donors or Lewis acids to stabilize and/or activate the carboxy group, thereby the hybrid catalyst 5 was designed as shown in Fig. 2. Indeed, both aminoboronic acid 18a and a dual catalyst consisting of an electron-deficient arylboronic acid 18b and a chiral aminothiourea 19 promoted the racemic and asymmetric hetero-Michael reactions of the α,β-unsaturated carboxylic acids 15, respectively.14

3.2. Developing Asymmetric Aza-Michael Addition

Since aza-Michael addition with nitrogen nucleophiles is an efficient method for synthesizing β-amino acid derivatives, we explored the intermolecular aza-Michael addition of O-
benzylohydroxylamine to carboxylic acid 15a using the hybrid catalysts 20–22. The reaction was performed in carbon tetrachloride in the presence of a 10 mol% catalyst and 4 Å molecular sieves (MS). Although aminoboronic acid 18a afforded the desired 1,4-adduct 16a in a low yield along with the bis-adduct 17 (Table 3, entry 1), the dual catalytic system using 18b and 19 gave 17 as a single product (entry 2). In contrast, the \( \text{N-tert-butoxycarbonyl (Boc)} \) catalyst 20 containing a carbamate N–H proton delivered the product 16a in a 40% yield with 58% ee without forming 17 (entry 3). Among the range of urea and thiourea hybrid catalysts 21 and 22a–d, electron-deficient thiourea 22d furnished the best results regarding yield and selectivity, obtaining 16a in an 83% yield with 90% ee (entries 4–8). Notably, the addition of the 4 Å MS was crucial for the efficient progress of this catalytic reaction.

To clarify the detailed mechanism of the catalytic reaction, the structure of the catalytically active borate complex was next investigated (Chart 3). The titration experiments revealed that different tetracoordinate borate complexes A and B were generated depending on the ratio of the catalyst and substrate (22b:15 = 1:1 vs. 1:2). Even in the presence of 10 equivalent (equiv) of 15, the presumed ternary complex B is predominant and is considered to play a crucial role in the stereo-determining step as shown in Fig. 3.

Based on the proposed mechanism, the addition of a different carboxylic acid (that does not function as a Michael receptor) to the reaction mixture might influence the stereoselectivity of 16. Therefore, the effect of benzoic acid was investigated for the 22b-catalyzed aza-Michael addition of 15b–g (Chart 4). In fact, the addition of benzoic acid enhanced the stereoselectivity of the products 16b–g from 90% ee to 94% ee without a notable decrease in yields when catalyst 22b was used in tetrachloroethylene. Among aromatic and aliphatic acids examined, benzoic acid was the best additive. The equivalence (1 equiv) of benzoic acid was also beneficial, and the yield and selectivity were reduced with more and fewer equivalents, respectively. Unlike the enzymes, the ATBA hybrid catalyst 22b enables the highly enantioselective aza-Michael addition of hydroxylamine derivatives to synthesize a variety of \( \beta \)-amino acids 16.

To rationalize the origin of high enantioselectivity, we then moved on to computational studies (Fig. 3). It is reasonable to consider that a similar complex C comprising 15 and benzoic acid would be also formed in the modified method. The carboxylate ligand of 15 could be synergistically activated by the thiourea N–H protons and boronic acid to enhance its electrophilicity as a Michael acceptor. On the other hand, the benzoate ligand of complex C could form a HB with the N–H proton of BnONH\(_2\). The benzoate ligand is suspected to be crucial in the transition state (as a Brønsted base) in bringing the nucleophile closer to the coordinated Michael acceptor. Moreover, the density–functional theory (DFT) calculations suggests that the second molecule of benzoic acid functions as a proton shuttle to accelerate the protonation of the resulting enolate anion as well as the deprotonation of BnONH\(_2\). Consequently, the nucleophile approaches from the si face of the

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**Table 3. Optimization of the Aza-Michael Addition**

| Entry | Catalyst | 16a Yield (%) | Ee (%) | 18 Yield (%) |
|-------|----------|---------------|--------|--------------|
| 1     | 18a      | 15            | —      | 7            |
| 2     | 18b + 19 | 0             | —      | 41           |
| 3     | 20       | 40            | 58     | 0            |
| 4     | 21       | 52            | 33     | 0            |
| 5     | 22a      | 81            | 80     | 0            |
| 6     | 22b      | 73            | 87     | 0            |
| 7     | 22c      | 65            | 78     | 0            |
| 8     | 22d      | 83            | 90     | 0            |

* a) Isolated yield after the treatment with TMSCHN\(_2\). b) Estimated by chiral HPLC analysis after the treatment with TMSCHN\(_2\).*
Michael acceptor in the s-trans conformation, leading to the major production of S-isomers.

Finally, two synthetic applications of the reaction were attempted. The first example was the formal asymmetric synthesis of sitagliptin. This was accomplished in four steps from the α,β-unsaturated carboxylic acid 15h without using any chiral auxiliary or protecting groups (Chart 5). The other example was the asymmetric synthesis of the N-hydroxy (S)-aspartic acid derivative via the Michael adduct 16i (70% yield, 86% ee), beginning from the fumarate monoesters 15i and O-[2-(trimethylsilyl)ethoxymethyl]hydroxylamine (SEMONH₂) as substrates.¹⁷) Since the known N-hydroxy-(S)-serine derivatives were diastereoselectively synthesized using chiral auxiliaries, this method is the first catalytic asymmetric synthesis of N-hydroxyamino acids. This catalytic method allows for the concise synthesis of natural and unnatural chiral synths.¹⁸)

3.3. Developing Asymmetric Thia-Michael Addition

Organosulfur compounds, validated as synthesis targets for novel bioactive compounds, exhibit a wide variety of functions in vivo. So far, the Michael addition of sulfur nucleophiles to various Michael acceptors has been used for producing sulfur-containing compounds. However, the thia-Michael addition to α,β-unsaturated carboxylic acids has not yet been achieved. To verify the utility of ATBA hybrid catalysts 22, we challenged to realize the first catalytic asymmetric thia-Michael addition to carboxylic acids 15 for the efficient construction of organosulfur compounds.¹⁹)

The conjugate addition of crotonic acid 15j and thiophenol were initially examined as model substrates. The reaction was conducted with hybrid catalyst 22b in carbon tetrachloride in the presence of 4Å MS to give the Michael adduct (S)-24a in a 90% yield with 41% ee (Table 4, entry 1). Notably, like the aza-Michael addition, the S-enantiomer was obtained as a major product. Furthermore, an interesting solvent effect was observed; the catalyst 22b preferentially provided the product with the S-configuration in nonpolar solvents, such as dichloromethane and hexane (entries 2 and 3). In sharp contrast, the same catalyst 22b produced the opposite enantiomer (R)-24a when the reaction was carried out in polar solvents, such as acetonitrile and acetone (entries 4 and 5). The unique chirality switch of the Michael adducts was discovered by simply switching solvents. This phenomenon may be used to construct a chemical library for drug discovery research requiring both enantiomers of drug candidates. Further screening of the catalysts revealed that the catalyst 22h in acetone resulted in the highest ee, while 22b showed the best results in carbon tetrachloride. The substituent at the para position significantly affected the stereoselectivity, but the substituent at the meta position of boronic acid exerted a minimum effect on the enantioselectivity (entries 7–10). In fact, (R)-24a was obtained...
with up to a 92% ee with catalyst 22h, in which the methoxy group was substituted at the para position.

The scope of the substrate was examined with regard to thiol and carboxylic acid. It was clarified that the arylthiols with electron-donating groups, such as a methoxy group, were suitable as sulfur nucleophiles. A variety of unsaturated carboxylic acids \textsuperscript{15} bearing different functional groups were tolerated. The two enantiomers were prepared with good yield and high ee by switching the solvent (Chart 6), regardless of the alkyl chain length. The reaction in carbon tetrachloride followed a similar trend to the aza-Michael addition. In the case of bulky substrates, the addition of benzoic acid efficiently restored the stereoselectivity of the product \((R)-24e\).

We next attempted to detect reaction intermediates by spectroscopic analysis. In carbon tetrachloride, the same complex \(C\) (consisting of 22b and two molecules of 15j) was generated (Chart 7). Thereafter, the nucleophile PhSH predominantly approaches from the si face of the \(s\)-trans formed Michael acceptor, favoring the \(S\)-isomer. In contrast, a distinct ternary complex \(D\) was formed in acetone in a 10:1 ratio of substrate 15j and catalyst 22b, since the electrospray ionization mass spectrometry detected a new molecular ion peak \((C_{29}H_{35}BN_3O_4S \rightarrow [M–H]^{-} 532.2440)\) but not one for complex \(C\) \((C_{29}H_{37}BN_3O_5S \rightarrow [M–H]^{-} 550.2552)\). These results strongly suggest that complex \(C\) loses one molecule of water in polar solvent to generate the complex \(D\), where the boron and the tertiary amine are connected by a B–N dative bond. In the transition state via \(D\), the thiol approaches from the \(re\) face of the Michael acceptor in an \(s\)-cis form, resulting in the predominant formation of \(R\)-isomers.

### 4. Total Synthesis of Avenaol

#### 4.1. Racemic Synthesis

Avenaol was isolated from the allelopathic plant black oat \((Avena strigosa\) Schreb.) as a non-typical strigolactone (SL) by Yoneyama and colleagues in 2014.\textsuperscript{20} Its structural features consist of a bicyclo[4.1.0]-heptanone skeleton, two lactone rings C and D, and four contiguous stereogenic centers. Like typical SLs such as strigol and orobanchol (Fig. 4), avenaol demonstrates potent germination-stimulating activity for \(Phelipanche ramosa\) seeds, but much lower activities for \(Striga hermonthica\) and \(Orobanche minor\) seeds. However, further studies are required to understand the relationship between the properties of avenaol and those of typical SLs. Although a variety of different strategies have been reported for the synthesis of typical SLs, there have been no reports to date for the synthesis of avenaol.
The main challenges associated with the synthesis of avenaol include the construction of a bicyclo[4.1.0]heptanone skeleton possessing an all-cis-substituted cyclopropane (B ring) and the stereocontrol at the C8 and C2’ positions of the C and D rings. This synthetic strategy of avenaol is shown in Chart 8. The core structure was constructed through the Rh-catalyzed intramolecular cyclopropanation of allene to aldehyde. This was followed by the discrimination of two diastereotopic primary alcohols of diol for the formation of the C ring and a final introduction of the γ-butenolide unit (D ring) into enol. This strategy effectively avoids the undesired ring opening of the cyclopropane ring and any intramolecular reactions.

The synthesis began with the preparation of the cyclization precursor from ester (Chart 9). The successive treatment of with the lithium salts of acetonitrile and imidazole-1-sulfonyl azide delivered the desired product in good yield. The key reaction of α-diazo-β-ketonitrile with Rh2(OAc)4 proceeded smoothly to give E-alkylidene cyclopropane as a single isomer. To convert into an all-cis-substituted cyclopropane like the hydrogenation over Pd on carbon was initially investigated. However, this only provided the undesired trans isomer as the major product, most likely because of the steric effect of the nitrile group. Next, the transition metal-catalyzed isomerization of the double bond using a directing group to reverse this selectivity was investigated.

Nitrile was transformed into the methyl adduct bearing a hydroxy group through the reductive manipulation. As expected, the subsequent treatment of with Crabtree’s catalyst (preactivated with H2) allowed for the olefin-isomerization to give aldehyde in a 61% yield with moderate diastereoselectivity (cis:trans = 2.7:1) together with an alcohol derivative (5% yield, cis:trans = 2.7:1). After multiple trials, the results demonstrated that the selectivity was significantly affected by the counter anion of the metal catalyst. Indeed, the Pfaltz modified Ir-catalyst containing a non-coordinating counter anion (i.e., BArF) gave the desired product in a cis:trans ratio of 10:1.

Next, the formation of the C ring was evaluated. Aldehyde was converted to diol by the introduction of an exo-methylene at the α position of the aldehyde, followed by hydroboration. Subsequently, a wide range of conditions to allow for the differentiation of the two hydroxy groups were screened. As a result, treatment of with pTsOH in the presence of thiophenol as a p-methoxybenzyl (PMB) scavenger led to the best yield of cyclic ether. To cleave the tetrahydropyran ring, was subjected to benzylation and subsequent hydroxylation with 2-(trifluoromethyl)dioxolane at −78 °C. This smoothly furnished ketone in excellent yield. The final stage of the total synthesis of avenaol involves the formation of an α-hydroxyketone and the introduction of the D ring. Ketone was efficiently converted.
into lactone 34 via the conventional six-step sequence. This was followed by the stereoselective dihydroxylation and the selective protection of the alcohol at C3, yielding alcohol 35 with excellent selectivity. The final transformation of 35 into avenaol was performed in four steps. After formylation of 35, O-alkylation with bromide 36 under basic conditions gave a 1:1 mixture of C2'-epimers. These epimers were subjected to Dess–Martin oxidation and deprotection with hydrogen fluoride (HF)·pyridine, completing the total synthesis of avenaol together with its C2'-epimer. The relative stereochemistry of the C2'-epimer was confirmed by X-ray crystallographic analysis. Based on the results that the spectroscopic data of synthetic avenaol (i.e., 1H, 13C-NMR, and high resolution MS) were identical to those of the natural sample, the proposed structure proved correct.

4.2. Enantioselective Synthesis of γ-Alkoxybutenolides Using Thiourea–Ammonium Hybrid Catalysts The racemic total synthesis of avenaol was successful, but stereocontrol at the C2' position was not achieved. To date, the D ring has been installed by the diastereoselective method using a chiral auxiliary and an asymmetric Pd-catalyzed reaction. Since no catalytic asymmetric acetalization for constructing chiral γ-alkoxybutenolides has been reported, we explored an enantioselective O-alkylation of achiral enol 37 with racemic γ-chlorobutenolide 38 using a chiral phase-trans-
fer catalyst (PTC) via the kinetic resolution of 38 (Chart 10). To obtain acetal 39 with high stereoselectivity, the catalyst would need to recognize both the nucleophile and electrophile through multipoint interactions. Therefore, a chiral thiourea–quaternary ammonium hybrid catalyst 40 was designed. In the expected transition state, the thiourea and ammonium moieties of the catalyst will form multiple noncovalent contacts with an in situ generated enolate and both the oxygen and chlorine atoms of the butanolide, respectively, thereby favoring an SN$_2$-type reaction of the enolate of 37 with one enantiomer of the racemic electrophile 38. Furthermore, if chloride anions generated during the reaction promote the racemization of γ-chlorobutenolide 38 through a reversible SN$_2$ reaction, dynamic kinetic resolution is expected to occur.

Initially, the reaction of enol 37a with racemic γ-chlorobutenolide 38 using cesium carbonate as a base (Chart 11) was investigated. 27) Preliminary investigations indicated that the uncatalyzed reaction was efficiently suppressed when chlorobenzene–water (20:1, v/v) was used as solvent. Therefore, the same reaction was carried out in chlorobenzene–water (20:1, v/v) in the presence of PTC 41a–d and 40a.28–30 Since 40a$^{31}$ (bearing a thiourea moiety) resulted in a better enantiomer ratio (er) of (+)-39a (46% yield, 66:34 er), an additional range of thiourea–ammonium hybrid catalysts 40b–l was examined. Notably, o-isopropylphenylthiourea 40b and the m-TsNH-benzyl derivative 40j demonstrated greatly improved stereoselectivities (85:15 er and 94:6 er, respectively). The reaction was efficiently complete even with a 1.1 equiv of racemic 38. This suggests that the dynamic kinetic resolution of rac-38 occurred during the reaction.

Next, the substrate scope was investigated under optimized conditions using 40j. Several substituents were introduced at the C5–C7 positions to perturb the electron density of the enol (Chart 12). Enols 37b–i, bearing both electron-donating and electron-withdrawing groups, underwent the O-alkylation with rac-38 to furnish the desired products 39b–i with good to high enantioselectivities (90:10–95:5 er). The yield decreased in the cases of 39e and 39f due to the reduced nucleophilicity and low solubility of the starting enols 37e and 37f. Although the dihydronaphthalenone 37j gave the coupling product 39j in a 45% yield with comparable enantioselectivity, the acyclic enol 37k and the phenol 37l resulted in low yield and poor selectivity. These results indicate that a cyclic structure attached to the enol was important to achieve good enantioselectivity. Notably, the developed conditions were also applicable to the enantiopure (+)-37m, resulting in the artificial strigolactone (2’R)-GR24$^{22}$ with good diastereoselectivity (92:8 er).

To further demonstrate the potential of the reaction, the asymmetric syntheses of SLs from the racemic enol precursors 37n and 37o (Chart 13) were attempted. When rac-37n was treated with rac-38 under optimized conditions, the desired product (+)-39n$^{24}$ was obtained in a 41% yield with 81:19 er together with (−)-ent-2’-epi-39n in a 34% yield with 85:15 er. These results indicate that the hybrid catalyst 40j precisely discriminates the C5 chirality of γ-chlorobutenolide, but not the stereochemistry of the ring juncture of nucleophile 37. Finally, the reaction was applied to racemate 37o to determine the absolute stereochemistry of avenal. After the same treatment of enol 37o with PTC 40j, the resulting alcohols 39o
and ent-2-epi-39o were converted to (+)-avenaol (43%, 81:19 er) and (−)-ent-2-epi-avenaol (24%, 96:4 er) according to the previously reported method. Since the circular dichroism spectrum of synthetic (+)-avenaol matched that of a natural sample, the absolute configuration of avenaol was determined to be 1R, 3S, 6R, 7S, and 2′R as is shown in Chart 13.

To rationalize the stereoselectivity of the reaction, the reaction mechanism shown in Fig. 5 was proposed. An ion pair intermediate between the cationic catalyst cat’ and the Z-enolate en’ derived from 37a was initially formed. The ion pair cat’ en’ then interacts with γ-chlorobutenolide to generate a ternary complex E, where the Z-enolate en’ likely changed the conformation to E-enolate. The subsequent S2-type O-alkylation of E-en’ with (R)-38 gave E-enol ether (R)-39a as the major product. This O-alkylation is likely a rate-determining step.

To elucidate the stereocontrol elements in this reaction, multiple possible transition states for the S2-type substitution pathways involving E-en’ and both (R)-38 and (S)-38 stereo-isomers of γ-chlorobutenolide were computationally explored. Consequently, the transition states TS(R) and TS(S) leading to the enantiomeric products (R)-39a and (S)-39a were obtained. The DFT calculations revealed that the enolate preferentially interacts with the o-isopropylphenylthiourea moiety of the catalyst (see the blue arrows in Fig. 5), whereas substrate 38 is activated by the tosylamide unit and the quaternary ammonium moiety (see the red arrows in Fig. 5). The most stable transition state involves the concerted C–O bond formation between (R)-38 and E-en’ and the C–Cl bond cleavage (TS(R)) in Fig. 5, leading to (R)-39a as the major product. In the transition state TS(R), the position of the enolate en’ is fixed via HB interactions between the carbonyl oxygen and one of the thiourea NH groups and via intermolecular π–stacking interactions. The electrophile (R)-38 is also bound to the catalyst by three different types of noncovalent contacts: (1) an N–H…Cl HB involving the tosylamide NH group; (2) electrostatic interaction with the positively charged ammonium unit (denoted R4N…O in Fig. 5); (3) a C–H…π type interaction with the aromatic ring of the tosyl group. In the reaction pathway towards the minor product (S)-39a, the lowest lying transition state [TS(S)] is predicted to be disfavored by 1.8 kcal/mol compared with TS(R). In addition, as chloride anions are present in the reaction system, fast racemization between (R)- and (S)-38 occurs. This is also supported by computations (the barrier for the S2-type racemization process is predicted to be only 15.5 kcal/mol). Consequently, the dynamic kinetic resolution of γ-chlorobutenolide 38 would proceed to produce (R)-39a as a major product. Overall, in this trifunctional catalytic system, the thiourea, quaternary ammonium, and tosylamide moieties played cooperative roles.

5. Conclusion

Innovative catalytic systems, including cyclic guanidine-type hydrogen-bond donor catalysts and thiourea-type hybrid catalysts, have been established. These catalysts enable unprecedented asymmetric reactions under mild and sustainable conditions. In addition, these catalysts afford an unprecedented synthetic strategy for practical and reliable drug synthesis and discovery research. To demonstrate their synthetic potential, this study accomplished the catalytic asymmetric synthesis of biologically important pharmaceuticals and natural products (i.e., atorvastatin, beraprost, sitagliptin, avenaol, and GR24). More importantly, the detailed mechanism of catalysis has been clarified via DFT calculations and spectroscopic analysis. Unique catalytic phenomena such as the dual role of benzoic acid as a boron ligand and a proton shuttle, the chirality switch of products via a solvent effect, and the dynamic

Chart 12. Scope and Limitations of Nucleophiles

Chart 13. Application to the Asymmetric Synthesis of SLs
kinetic resolution of a racemic electrophile in an $S_2$-type reaction have been discovered. The concept of multifunctional hybrid catalysts described in this study will expose new areas of catalysis and contribute to further developments in the research field.

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