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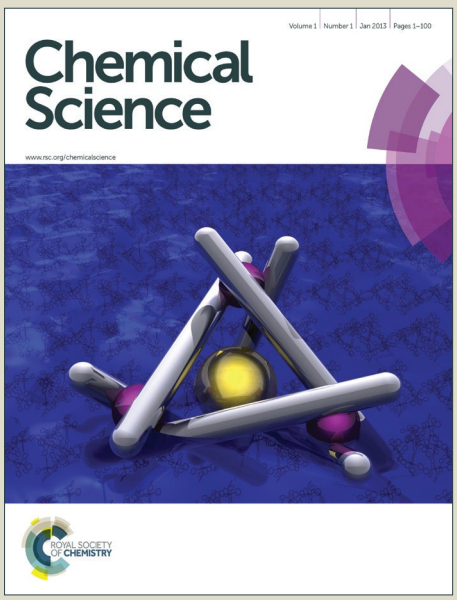

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ARTICLE

Highly Enantioselective Construction of Tertiary Thioethers and Alcohols via Phosphine-Catalyzed Asymmetric γ-Addition reactions of 5*H*-Thiazol-4-ones and 5*H*-Oxazol-4-ones: Scope and Mechanistic Understandings

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Phosphine-catalyzed highly enantioselective γ-additions of 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones to allenoates have been developed for the first time. With the employment of amino-acid derived bifunctional phosphines, a wide range of substituted 5*H*-thiazol-4-one and 5*H*-oxazol-4-one derivatives bearing heteroarom (S or O)-containing tertiary chiral centers were constructed in high yields and excellent enantioselectivities. The reported method provides a facile access to enantioenriched tertiary thioether/alcohols. The mechanism of γ-addition reaction was investigated by performing DFT calculations, and the hydrogen bonding interactions between the Brønsted acid moiety of the phosphine catalysts and the "C=O" unit of donor molecules were shown to be crucial in asymmetric induction.

1. Introduction

Organosulfur compounds are important molecular architectures in synthetic organic chemistry[1] and chemical biology.[2] Therefore, it is not surprising that many methods have been devised in recent years to access optically active thiol derivatives. Common approaches include: conjugate addition of thiols,[3] employment of sulfur-containing pronucleophiles,[4] kinetic resolution of racemic thiols,[5] and electrophilic sulfenylation reactions.[6] In this context, catalytic synthesis of chiral tertiary thiols is a challenging task and remains largely unexplored.[7] Analogously, tertiary alcohol-containing structures are of great importance in the biological sciences and pharmaceutical industry,[8] and asymmetric synthesis of chiral tertiary alcohols is an intensively investigated area.[9] A few selected biologically important tertiary thiols and alcohols are illustrated in Figure 1.[10] At the outset of this research, we aimed to devise a versatile catalytic approach that would allow us to access both tertiary thiols and alcohols in an enantioselective manner.

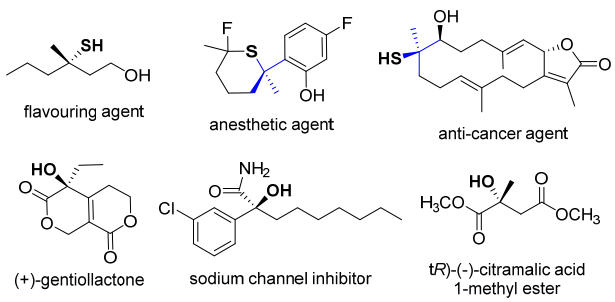
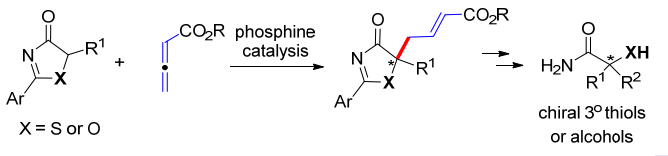


Figure 1. Representative bioactive tertiary thiol(ether)s and alcohols.

To develop a method for asymmetric synthesis of tertiary thiol molecules, it seems ideal to employ a readily accessible prochiral organosulfur compound. 5*H*-Thiazol-4-one and its derivatives, found useful in medicinal chemistry,[11] are suitable donors; the acidic protons at 5-position can be readily removed to facilitate their reactions with various electrophiles. Surprisingly, 5*H*-thiazol-4-ones were rarely used in asymmetric synthesis, and there were only three examples to date describing their applications in asymmetric catalysis. Palomo and co-workers reported a Brønsted base-catalyzed Michael addition of thiazolones to nitroalkenes[12a] and α'-silyloxy enone,[12b] respectively, for the synthesis of tertiary thiols. Very recently, Hartwig disclosed an Ir-catalyzed allylation of 5*H*-thiazol-4-ones to form enantioenriched tertiary thioethers.[12c] We envisioned that careful selection of electrophilic reaction partners and catalytic systems, in combination with the utilization of pronucleophilic 5*H*-thiazol-4-ones, will lead to the discovery of novel synthetic methods for asymmetric construction of tertiary thiols. Moreover, given the ready availability of the analogous 5*H*-oxazol-4-ones,[13] we anticipate the methodology developed for thiol synthesis can be easily adapted to include α-oxygenated carboxylate surrogates, thus allowing facile preparation of chiral tertiary alcohols as well.



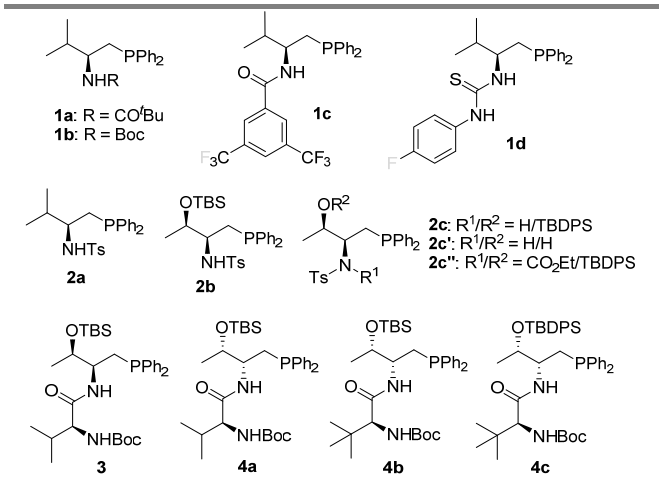
Scheme 1. Construction of tertiary thiols/alcohols via phosphine-catalyzed γ-additions of 5*H*-thia(oxa)zol-4-ones.

Our group has been actively investigating asymmetric phosphine catalysis[14] in the past few years. We designed a series of amino acid-based bifunctional phosphine catalysts, and demonstrated their applications in a wide range of asymmetric transformations, including: (aza)-MBH reactions,[15] [3+2], [4+2], and [4+1] annulations,[16] allylic alkylation,[17] and Michael addition.[18] Very recently, we disclosed the utilization of 2,3-butadienoates in phosphine-catalyzed enantioselective γ-addition reactions.[19,20] To further expand phosphine-mediated asymmetric reactions, we envisaged that 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones could serve as valuable donors in phosphine-catalyzed γ-addition reactions to allenoates (Scheme 1). The chiral heteroatom-containing adducts formed would have masked functionalities, and can be manipulated easily to give tertiary thiols/thioethers and alcohols.

In this article, we disclose the first utilization of 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones in phosphine-catalyzed asymmetric γ-addition reactions, and the products can be readily converted to optically enriched tertiary thioethers and alcohols. In addition, we have also carried out DFT calculations to gain insights into the reaction mechanism and understand the origin of stereochemical outcome of the reaction.

2. Results and discussion

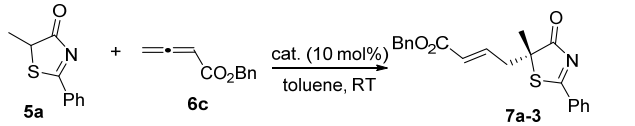
2.1 Phosphine-catalyzed enantioselective γ-addition of 5*H*-thiazol-4-ones. In the past few years, amino acid-based bifunctional phosphines have been shown to be very powerful in phosphine catalysis. In this study, readily available L-valine and L-threonine were chosen as the starting chiral skeletons for the preparation of phosphine catalysts. By installing different hydrogen bond donating groups and introducing various *O*-silyl protective groups, we prepared a wide range of amino acid-derived bifunctional phosphines (Scheme 2), which were used for subsequent studies.



Scheme 2. Phosphine catalysts investigated.

We began our investigations by choosing 5-methyl-2-phenylthiazol-4(5*H*)-one **5a** and allenoate **6c** as substrates to evaluate catalytic effects of phosphine catalysts for the projected γ-addition (Table 1). To our delight, all the bifunctional phosphines could effectively promote the reaction. Among L-valine-derived phosphines, sulfonamide–phosphine **2a** was found to be most efficient (entries 1–5). L-Threonine-derived phosphine sulfonamide catalysts (**2b** & **2c**) were then employed, and the enantioselectivity of the reaction could be improved to 89% ee (entries 6–7). Dipeptide phosphines were found to be less effective (entries 8–11).

Table 1. Enantioselective γ-addition of 5*H*-thiazol-4-one **5a** with allenoate **6c** catalyzed by different chiral phosphines[a]

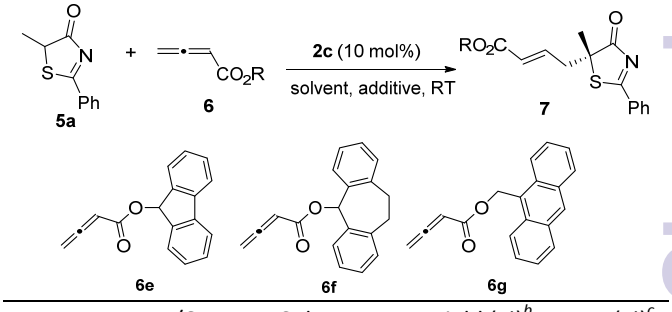


Entry	Cat.	Time (h)	Yield (%)[b]	ee (%)[c]
1	1a	12	86	10
2	1b	12	90	62
3	1c	12	86	34
4	1d	12	92	34
5	2a	12	91	66
6	2b	12	90	78
7	2c	12	95	89
8	3	12	88	47
9	4a	12	92	-57
10	4b	12	88	-65
11	4c	12	92	-68

[a]Reactions were performed with **5a** (0.1 mmol), **6c** (0.12 mmol) and the catalyst (0.01 mmol) in toluene (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

Subsequently, we further optimized the reaction conditions by varying the ester moiety in the allenoate structure (Table 2, entries 1–8). Among all the allenoates examined, the dibenzosuberyl ester proved to be the best, and the ee value of the reaction could be further improved to 91% (entry 6). At last, solvent screening revealed that diethyl ether was the solvent of choice, and the desired product was obtained in 97% yield and with 95% ee under the optimized conditions (Table 2, entries 9–12). The use of different molecular sieves as additives did not result in further improvement in enantioselectivity (entries 13–15). In addition lowering the reaction temperature resulted in a significant decrease in reactivity coupled with reduced enantioselectivity (entry 16).

Table 2. Optimization of reaction conditions[a]



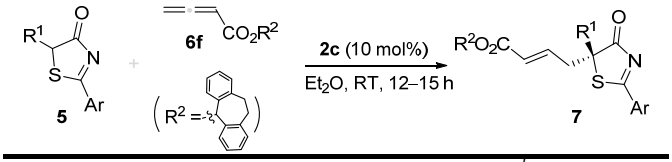
Entry	R/**6**	Solvent	Yield (%)[b]	ee (%)[c]

1	Et/**6a**	toluene	95	87
2	^{t}Bu/**6b**	toluene	95	88
3	Bn/**6c**	toluene	95	89
4	$CHPh_2$/**6d**	toluene	86	90
5	**6e**	toluene	88	70
6	**6f**	toluene	96	91
7	**6g**	toluene	93	87
8	Ph/**6h**	toluene	91	57
9	**6f**	xylene	95	93
10	**6f**	Et_2O	97	95
11	**6f**	$CHCl_3$	94	83
12[d]	**6f**	CH_2Cl_2	87	92
13[e]	**6f**	toluene	97	94
14[f]	**6f**	toluene	97	94
15[g]	**6f**	toluene	96	94
16[h]	**6f**	toluene	86	90

[a]Reactions were performed with **5a** (0.1 mmol), **6** (0.12 mmol) and **2c** (0.01 mmol) in the solvent specified (1.0 mL) at room temperature for 12 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The reaction was stirred for 15 h. [e]The 3Å-MS was added. [f]The 4Å-MS was added. [g]The 5Å-MS was added. [h]The reaction was stirred at 0 °C for 36 h.

Having established the optimal reaction conditions, the substrate scope for γ-addition of thiazolones to allenoates was then evaluated (Table 3). A wide range of 5-alkyl substituted 5*H*-thiazol-4-ones could be employed, the reaction was insensitive to the length of the alkyl chain, and both linear and branched alkyl groups were well tolerated (entries 1–10). In addition, benzyl and 2-(naphthalen-2-yl)-substituted thiazolones also proved to be suitable substrates (entries 11–12).

Table 3. Substrate scope for the enantioselective γ-addition of 5*H*-thiazol-4-ones to allenoates[a]

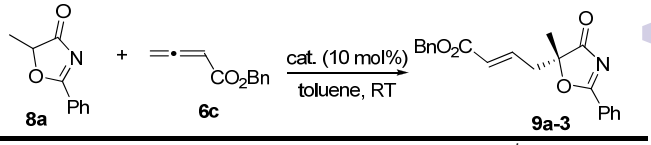


Entry	Ar/R^1	Pro.	Yield (%)[b]	ee (%)[c]
1	Ph/Me	**7a**	97	95
2	Ph/Et	**7b**	95	94
3	Ph/*n*-Pr	**7c**	97	94
4	Ph/*i*-Pr	**7d**	92	92
5	Ph/*n*-Bu	**7e**	94	94
6	Ph/*iso*-Bu	**7f**	89	88
7	Ph/*n*-C_6H_{13}	**7g**	96	94
8	Ph/$CH(CH_2)_5$	**7h**	95	93
9	Ph/$(CH_2)_2SCH_3$	**7i**	93	90
10	Ph/*n*-$C_{10}H_{21}$	**7j**	86	93
11	Ph/Bn	**7k**	90	92
12	2-Nap/Me	**7l**	96	89

[a]Reactions were performed with **5** (0.1 mmol), **6f** (0.12 mmol) and **2c** (0.01 mmol) in Et_2O (1.0 mL) at room temperature for 12–15 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

2.2. Enantioselective γ-addition of 5*H*-oxazol-4-ones. With the established protocol for asymmetric γ-addition of 5*H*-thiazol-4-ones in hand, we next targeted to access analogous α-oxygenated carboxylate surrogates by employing 5*H*-oxazol-4-ones. This task could be challenging as examples of having both sulfur- and oxygen-substituted substrates in the same report are rare.[12c] We hypothesized that high tunability of our amino acid-based phosphine systems may provide a practical solution to this problem. The same set of phosphine catalysts were screened for the γ addition of 5*H*-oxazol-4-ones to allenoate 6c, and the results are summarized in Table 4. The best catalyst 2c for the previous addition of 5*H*-thiazol-4-ones only afforded moderate enantioselectivity (entry 1). Switching to dipeptide phosphines resulted in highly effective catalytic systems. While *O*-TBDPS-L-Thr-L-*tert*-Leu-based 3 led to the desired adduct with slightly improved ee value, *O*-silyl-D-Thr-L-*tert*-Leu-derived phosphines offered excellent catalytic effects (entries 9–11). Finally, phosphine 4c was found to be the best catalyst, affording 9a in 95% yield and 76% ee (entry 11).

Table 4. Screening catalyst for enantioselective γ-addition of 5*H*-oxazol-4-one **8a** with allenoate **6c**[a]



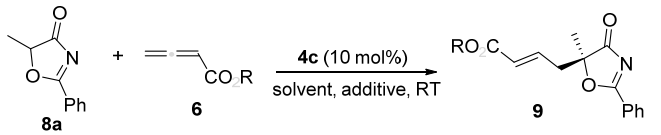
Entry	Cat.	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2c**	12	89	65
2	**1a**	12	89	60
3	**1b**	12	91	63
4	**1c**	12	92	34
5	**1d**	12	87	12
6	**2a**	12	89	58
7	**2b**	12	88	63
8	**3**	12	93	59
9	**4a**	12	94	-70
10	**4b**	12	94	-73
11	**4c**	12	95	-76

[a]Reactions were performed with **8a** (0.1 mmol), **6c** (0.12 mmol) and the catalyst (0.01 mmol) in toluene (1.0 mL) at room temperature for 12 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

To further improve the enantioselectivity, we next optimized the ester moieties in allenoates (Table 5). Among different allenoate esters, the dibenzosuberyl ester was most ideal, affording the desired adduct in 96% yield and 86% ee (entry 6). Solvent screening

identified diethyl ether as the most suitable solvent for the reaction. When the reaction was performed in the presence of 3Å molecular sieves in diethyl ether, the γ-addition product was obtained in 97% yield and with 92% ee (entry 14).

Table 5. Optimization of reaction conditions for γ-addition of 5*H*-oxazol-4-one[a]

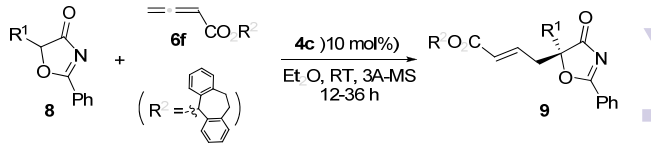


Entry	Allenoate	Solvent	Yield (%)[b]	ee (%)[c]
1	**6a**	toluene	93	77
2	**6b**	toluene	95	82
3	**6c**	toluene	95	76
4	**6d**	toluene	96	84
5	**6e**	toluene	95	84
6	**6f**	toluene	96	86
7	**6g**	toluene	85	79
8	**6h**	toluene	89	67
9	**6f**	xylene	95	85
10	**6f**	Et_2O	97	88
11	**6f**	$CHCl_3$	92	46
12	**6f**	CH_2Cl_2	90	50
13	**6f**	CH_3CN	82	67
14[d]	**6f**	Et_2O	97	92
15[e]	**6f**	Et_2O	96	91
16[f]	**6f**	Et_2O	96	90
17[d,g]	**6f**	Et_2O	86	91

[a]Reactions were performed with **8a** (0.1 mmol), **6** (0.12 mmol) and **4c** (0.01 mmol) in the solvent specified (1.0 mL) at room temperature overnight. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]3Å Molecular sieve was added. [e]4Å Molecular sieve was added. [f]5Å Molecular sieve was added. [g]The reaction was stirred at 0 °C for 20 h.

Under the optimal reaction conditions, the reaction was applicable to a wide variety of 5-alkyl substituted 5*H*-oxazol-4-ones. As shown in Table 6, the length of alkyl chains can be varied, and both linear and branched alkyl groups could be employed, and high yields and excellent ee values were attainable in all cases (entries 1–10). When 5-benzyl substrate was used, the enantioselectivity of the reaction dropped slightly (entry 11), may due to the unfavourable aromatic interactions induced by the Bn group. The absolute configuration of the γ-addition products was assigned by comparing the optical rotation of a derivative of **9b** with the value reported in the literature.[21]

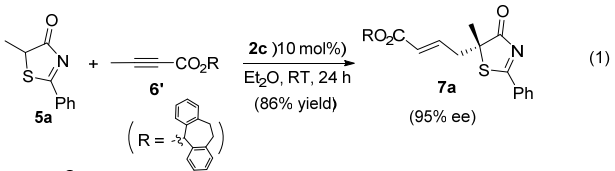
Table 6. Substrate scope for the enantioselective γ-addition of 5*H*-oxazol-4-ones to allenoates[a]

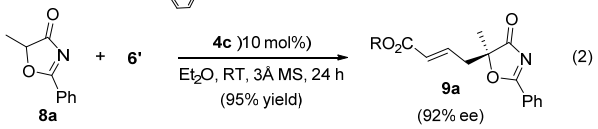


Entry	R^1	Time (h)	**9**/Yield (%)[b]	ee (%)[c]
1	Me	12	**9a**/97	**92**
2	Et	12	**9b**/93	93
3	*n*-Pr	12	**9c**/94	92
4	*i*-Pr	20	**9d**/93	93
5	*n*-Bu	12	**9e**/95	91
6	*iso*-Bu	12	**9f**/96	93
7	*t*-Bu	36	**9g**/89	97
8	$n\text{-}C_6H_{13}$	20	**9h**/94	93
9	$(CH_2)_2SCH_3$	12	**9i**/98	94
10	$n\text{-}C_{10}H_{21}$	20	**9j**/91	92
11	Bn	20	**9k**/94	81

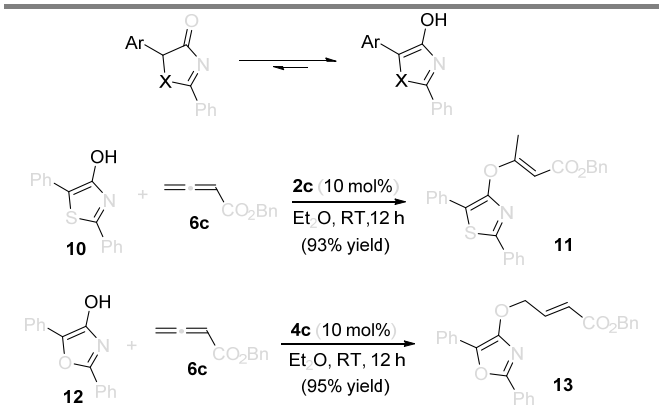
[a]Reactions were performed with **8a** (0.1 mmol), **6** (0.12 mmol) and **4c** (0.01 mmol) in the solvent specified (1.0 mL) at room temperature overnight. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]3Å Molecular sieve was added. [e]4Å Molecular sieve was added. [f]5Å Molecular sieve was added. [g]The reaction was stirred at 0 °C for 20 h.

2.3. Scope of substrates and synthesis of tertiary thioethers and alcohols. Alkynes are common starting materials in organic synthesis, and the reaction here could be extended to alkyne substrates. Alkynoate (**6'**) could be employed, instead of allenoates, in the γ-addition reactions of both 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones. Although the reactions were slower, chemical yields and enantioselectivities were the same [Eq. (1) and Eq. (2)].





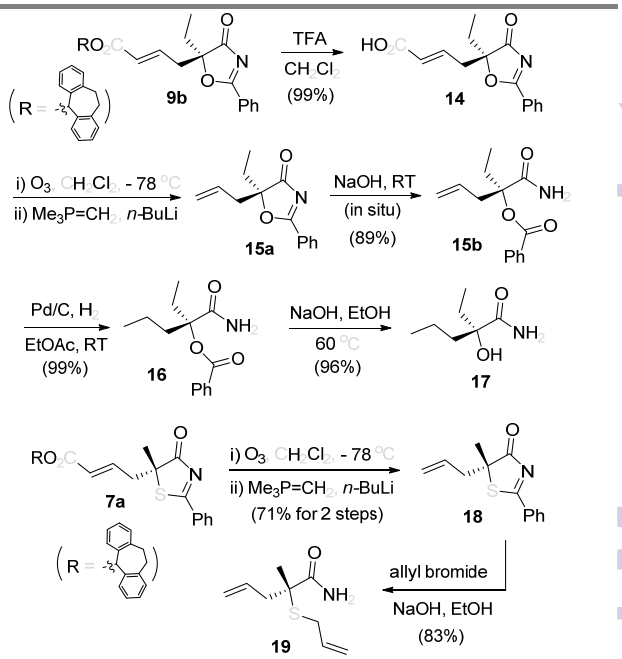
For thia(oxa)zolone substrates, inclusion of 5-aryl-substituted thiazol-4-ones and oxazol-4-ones was unsuccessful. Thia(oxa)zolones are known to exist in tautomeric forms as thia(oxa)zoles,[22] and the presence of 5-aryl group makes enol forms far more dominating. Indeed, the γ-addition products were not observed when 5-aryl substituted substrates were used. Instead, *O*-attack of the tautomeric thiazole/oxazole to allenoates took place, and the corresponding achiral adducts were obtained in high yields (Scheme 3).



Scheme 3. Reactions of 2,5-diphenyl-thiazol-4-ol **10** and 2,5-Diphenyl-oxazol-4-ol **12** with allenoate **6c**.

The γ-addition products obtained possess a tertiary stereogenic center linked to a buried heteroatom, and they are valuable precursors for convenient synthesis of enantiomerically enriched tertiary thiols/alcohols. As illustrated in Scheme 4, adduct **9b** was converted to allyl oxazolone **15a**, which was then treated with base to effect a ring opening, leading to the formation of tertiary alcohol **15b** in excellent yield. Reduction of double bond and cleavage of ester afforded tertiary α-hydroxy acid derivative **17**, which has an ethyl and a propyl groups presenting in the tertiary alcohol structure. Similarly, thiazolone **7a** was transformed to allyl-substituted **18**, which was readily converted to an enantiomerically enriched tertiary thioether **19** via a base-catalyzed ring opening.[23]

2.4. Mechanistic insights and DFT calculations. Despite the popularity of phosphine-catalyzed organic reactions, the mechanistic investigations remained very limited; a few theoretical studies appearing in the literature were disclosed by the groups of Yu,[24a-c] Kwon,[24d,e] and others[24f-h] We hypothesized that the hydrogen-bonding interactions between the Brønsted acid moiety of the phosphine catalyst and donor molecules are essential for inducing enantioselectivity in our early reports on bifunctional phosphine catalyzed Michael and γ-addition reactions,[18,20] and we believe such interactions are also crucial in our current reaction systems. The mechanism of γ-addition of 5*H*-thiazol-4-one to allenoate is shown in Scheme 5, which follows the general mechanism described in the literature for γ-addition reaction.[19,20] The reaction is initiated by the nucleophilic attack of the phosphorus atom on allenoate to form intermediate **B**, which is weakly basic. Deprotonation of donor 5*H*-thiazol-4-one by **B** then affords the corresponding enolate, which subsequently attacks the γ-carbon of the allenoate to give intermediate **E**. Proton transfer takes place to afford **18**,[20] and this is followed the elimination of the phosphine catalyst to furnish the final addition product. We propose that hydrogen bonding interaction between sulfonamide N–H and the thiazolone enolate dictates its addition to the C–C double bond, which is the key step for asymmetric induction.



Scheme 4. Elaboration of γ-addition adducts into enantioenriched tertiary alcohols/thioethers.

In an effort to provide theoretical support to the proposed reaction mechanism and to rationalize the origin of enantioselectivity, detailed density functional theory (DFT) calculations were conducted. DFT methods as implemented in the Gaussian 09[25] program have been employed to study the model reaction involving reactants 5*H*-thiazol-4-ones **5a**, allenoate **6c** and catalyst **2c**. All the stationary points are optimized at the B3LYP[26]/6-31G (d) level[27] of theory. The vibrational frequencies were computed at the same level of theory to determine whether the optimized structure is at an energy minimum or a transition state and to evaluate the corrections of enthalpy and Gibbs free energy. Solvent effects were computed by the IEFPCM[28] salvation model at the M11[29] /6-311+G (d)[30] and B3LYP-D3[31] /6-311+G (d) levels of theory using the gas phase optimized structures. The conclusions are similar with both methods, and the B3LYP-D3 calculated Gibbs free energies in toluene are discussed in the text.

The calculated Gibbs free energy profiles for phosphine-catalyzed γ-addition of **6c** and **5a** are summarized in Figure 2 (blue line). As proposed, the reaction is initiated by the nucleophilic attack o phosphine catalyst **2c** on allenoate **6c** via transition state **Ts-1** with a barrier of 19.8 kcal/mol. This process is facilitated by the NH···C hydrogen bond to bring the phosphine and the allene group to proximity. A zwitterionic intermediate **B** is first formed with 9.4 kcal/mol endothermic reversibly. Subsequent proton transfer between intermediate **B** and reactant **5a** takes place via transitior **Ts-2** with a barrier of 14.4 kcal/mol (an overall barrier of 23.8 kcal/mol). The nucleophilic attack can then take place in two possible pathways: the *Re*-face attack occurs through transition state **Ts4-*Re*** with a barrier of 7.8 kcal/mol to give intermediate E with *R*-configuration ((*R*)-**E**); and the alternative *Si*-face attack proceeds via transition state **Ts4-*Si*** with a barrier of 9.7 cal/mol, 1.9 kcal/mol higher than that of **Ts4-*Re***, leading to the intermediate with *S*-configuration ((*S*)-**E**). The corresponding addition product **7a**

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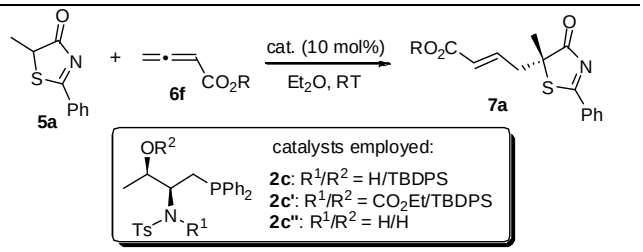
can be generated by the proton transfer and elimination of the catalyst, the pathway similar to those reported by Yu and co-workers.[24a-c] These observations suggest that the enantioselectivity is determined by the nucleophilic attack step and a value of 92% ee predicted by the B3LYP-D3 method based on the energy difference of **Ts4-*Re*** and **Ts4-*Si*** is in good agreement with the experimental result, where the *R*-product was formed preferentially (89% ee, entry 7 in Table 1). When the sulfur is replaced by oxygen (5-methyl-2-phenyloxazol-4(5*H*)-one (**8a**)), the B3LYP-D3 calculations predict a value of 47% ee for *R*-isomer (based on the energy difference of 0.6 kcal/mol between transition states **Ts5-*Re*** and **Ts5-*Si***), consistent with the experimental observations (65% ee, entry 1 in Table 4).

Upon evaluating transition states **Ts4-*Re*** and **Ts4-*Si*** (Figure 3), it was found that the bond lengths for forming C1–C2 bond are similar as well as the distances of the hydrogen bonds between H3 and O2 (about 1.8 Å). However, the short H2···C3 distance of 3.04 Å in **Ts4-*si*** suggests the repulsion between the phenyl group of reacting thiazolone and one of the phenyl groups of the phosphine catalyst, resulting in a higher transition state barrier. To better illustrate the steric repulsions in the nucleophilic addition step, 2D contour map along the z-axis (defined as the forming C–C bond) of the van der Waals[32] surface of **Ts4-na** is plotted (Figure 4), representing the nucleophile moiety of transition state **Ts4-*Re*** without the thiazolone substrate. When the thiazolone group is deprotonated and bound to the catalyst via the N-H···O hydrogen bonding for the formation of C–C bond along the z-axis, the steric hindrance for the *Re*-face attack (labelled as *R*) is smaller than that for the *Si*-face one (labelled as *S*). As such, the *Re*-face becomes more favorable.

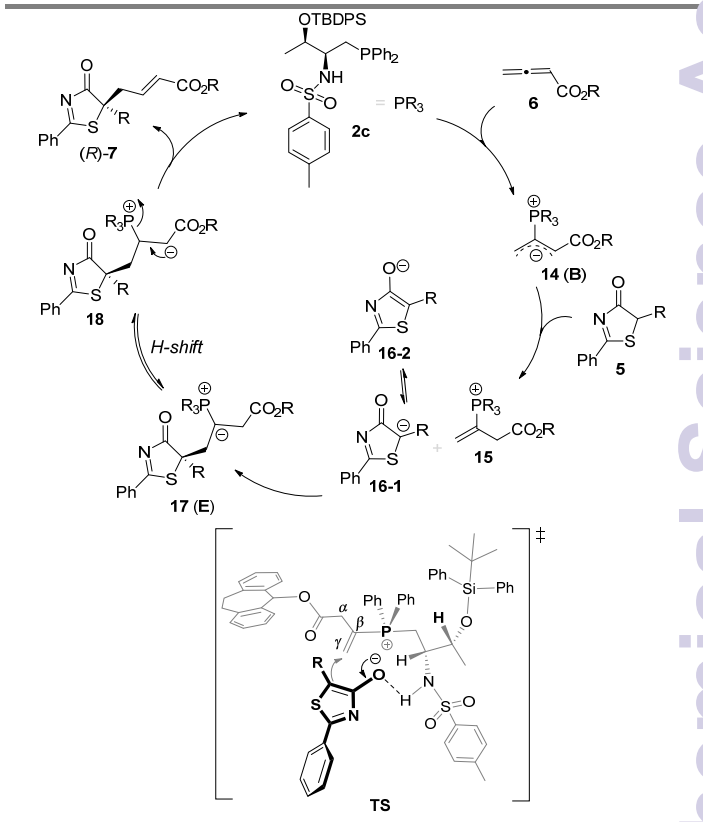
Experimental confirmation. The importance of hydrogen bonding interactions for asymmetric induction has been clearly demonstrated in the above computational studies. Sulfonamide **2c** and its close structural analogs **2c'** and **2c''** were synthesized and tested for the γ-addition of 5*H*-thiazol-4-one **5a** to allenoate **6f** (Table 7). The blockage of sulfonamide N–H led to a dramatic decrease in reactivity and enantioselectivity (entry 2). When sterically hindered *O*-silyl group was replaced by a free OH, not only enantioselectivity, but also reactivity of the reaction decreased significantly (entry 3), suggesting that the bulky silyl group may be crucial for locking the transition state geometry to differentiate the *Re*-and *Si*-face attacks.

Table 7. Asymmetric γ-addition of 5*H*-thiazol-4-one **5a** promoted by different phosphines[a]



entry	catalyst	t(h)	yield (%)[b]	ee (%)[c]
1	**2c**	12	97	95
2	**2c'**	30	82	37
3	**2c''**	24	95	53

[a]Reactions were performed with **5a** (0.1 mmol), **6f** (0.12 mmol) and the catalyst (0.01 mmol) in Et_2O (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.



Scheme 5. Proposed mechanism for **2b**-catalyzed γ-addition of 5*H*-thiazol-4-one to allenoate.

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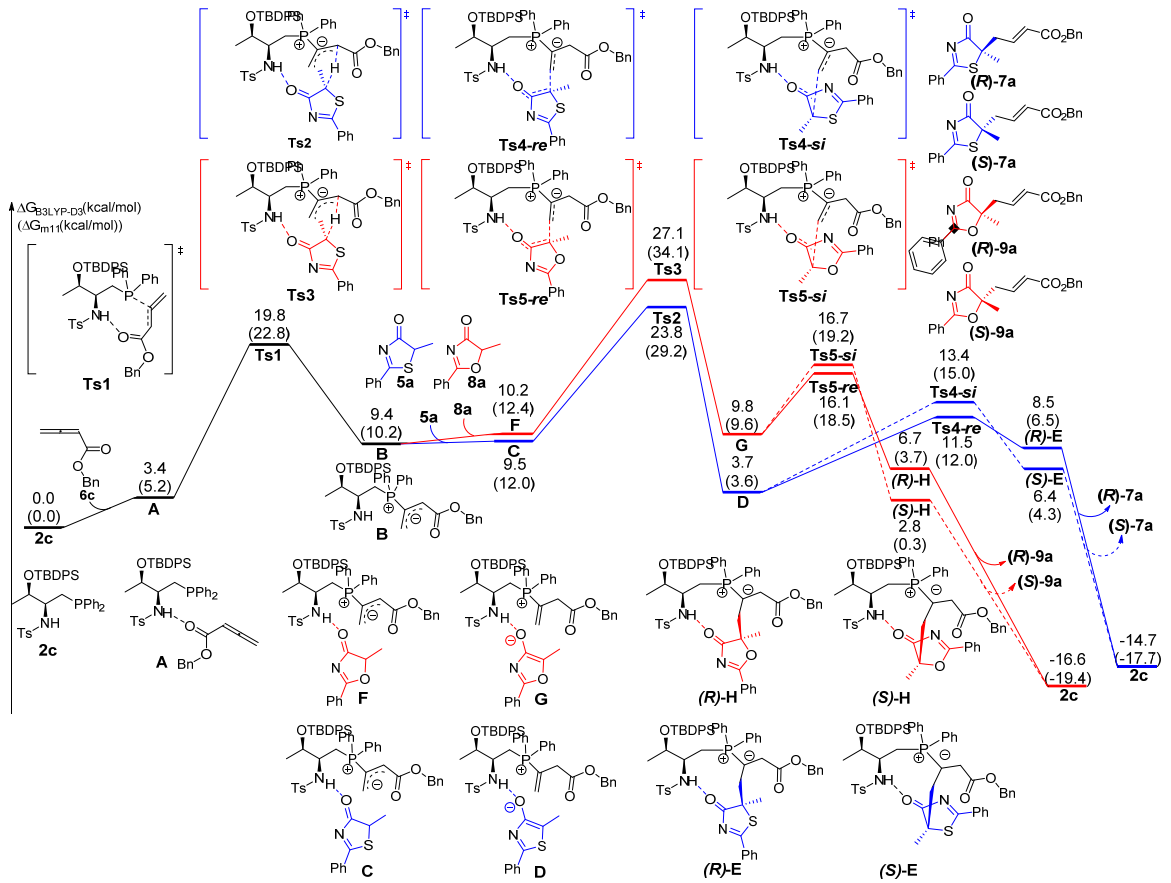

Figure 2. The DFT computed energy surfaces of the γ-addition reaction of **5a** and **8a** to allenoate **6c**. The values given by kcal/mol are the B3LYP-D3 calculated relative free energies in toluene. The values in parentheses are the M11 calculated relative free energies in toluene.

3. Conclusions

In summary, we have developed the first phosphine-catalyzed highly enantioselective γ-addition of 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones to 2,3-butadienoates. In the presence of amino acid-derived bifucntional phosphine catalysts, chiral thiazolones and oxazolones with a heteroatom (S or O)-containing tertiary chiral center were obtained in high yields and with excellent enantioselectivities. The optically enriched adducts are synthetically valuable, enabling facile synthesis of optically enriched tertiary alcohols and thioethers. The method described in this report represents a method for rapid access to enantioenriched tertiary alcohol and thiol derivatives bearing an allylic chain, and may find wide applications in synthetic organic chemistry. DFT calculations for mechanistic understandings revealed that the observed enantioselectivity results from a combination of three factors: 1) the hydrogen-bonding interaction between the amino moiety of the phosphine catalyst and the "C=O" unit of the thiazolone to activate the Michael donor, 2) the N-H···O interaction and the bulky *O*-silyl group to lock the conformation, and 3) the phenyl group of the thiazolone to differentiate the stereochemistry. It is noteworthy that this is the first complete theoretical study for phosphine-catalyzed γ-addition reactions. The theoretical results presented here are expected to offer new insight into the mechanisms of other phosphine-catalyzed asymmetric reactions, particularly those triggered by amino acid-derived phosphine catalysts.

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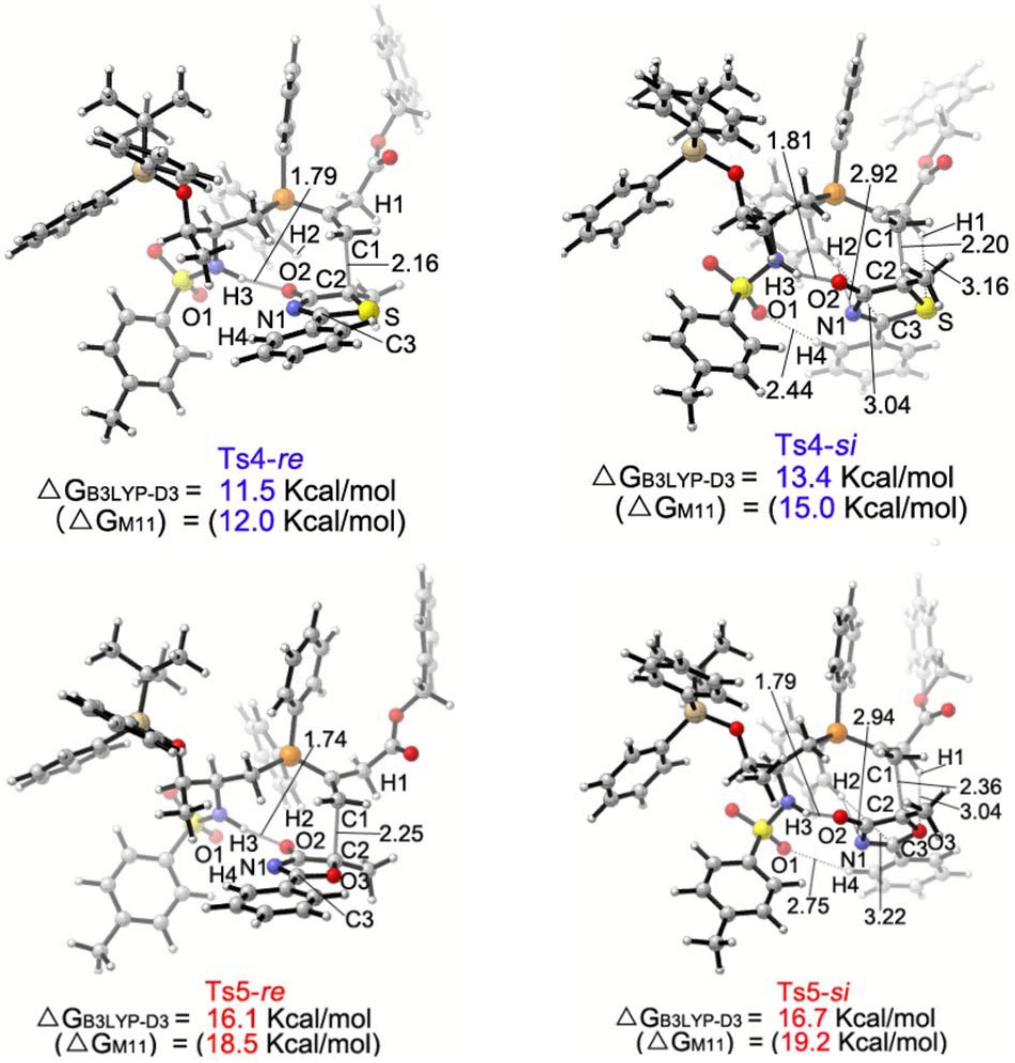

Figure 3. Geometries of **Ts4-re**, **Ts4-si**, **Ts5-re** and **Ts5-si**. The values of bond lengths are given by angstrom.

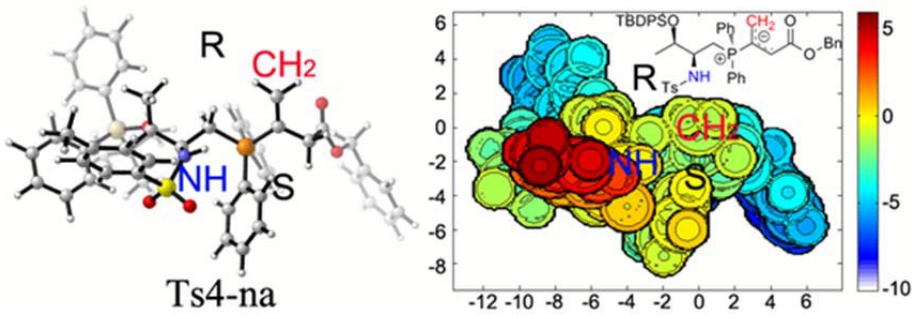

Figure 4. 2D contour maps of the van der Waals surface of catalyst **2c** and allenoate **6c**. Distances are valued in Å. C atom of CH_2 group (labled by red "CH_2") is located at the origin of the coordinate system in the contour maps. Contour line of zero is defined as in the same plane of the C atom. Negative distance (blue) indicates the atoms on complex are farther away from substrate; positive distance (red) indicates the atoms on complex are closer to substrate.

Notes and references

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