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Title: Enantioselective Construction of Spiro[chroman-thiazolones]: Bifunctional Phosphonium Salt-Catalyzed [2 + 4] Annulation between 5-Alkenyl Thiazolones and ortho-Hydroxyphenyl-Substituted para-Quinone Methides

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Enantioselective Construction of Spiro[chroman-thiazolones]: Bifunctional Phosphonium Salt-Catalyzed [2 + 4] Annulation between 5-Alkenyl Thiazolones and *ortho*-Hydroxyphenyl-Substituted *para*-Quinone Methides

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Abstract. The enantioselective formal [2 + 4] annulation of 5-alkenyl thiazolones with hydroxyl-substituted *para*-quinone methides was disclosed by dipeptide-based phosphonium salt catalysts. A wide range of functionalized spiro-chroman-thiazolone molecules bearing three contiguous 3° and/or 4° stereocenters were readily constructed in high yields with excellent stereoselectivities (>20:1 dr and up to >99.9% ee) under low catalyst loading and mild reaction conditions. The practicality and utility of this protocol were demonstrated by the scaled-up preparation and elaborations of product.

Keywords: bifunctional phosphonium salt catalysis; spiro-chroman-thiazolone; [2 + 4] annulation; 5-alkenyl thiazolones; *para*-quinone methides.

Thiazole skeletons, especially optically pure thiazol-4-one units bearing a tetrasubstituted carbon stereocenter, are prominent building blocks not only in many biologically active natural products but also in numerous medicinally important agents.[1,2] For instance, compounds **A** and **B** are commonly considered as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors, and compound **C** demonstrates antibacterial activities (Figure 1a).[3,4] Not surprisingly, a considerable amount of effort has thus been directed toward the development of new technologies to access these frameworks.[5] As a consequence, the catalytic asymmetric annulation of 5-alkenyl thiazolones with another appropriate partner is

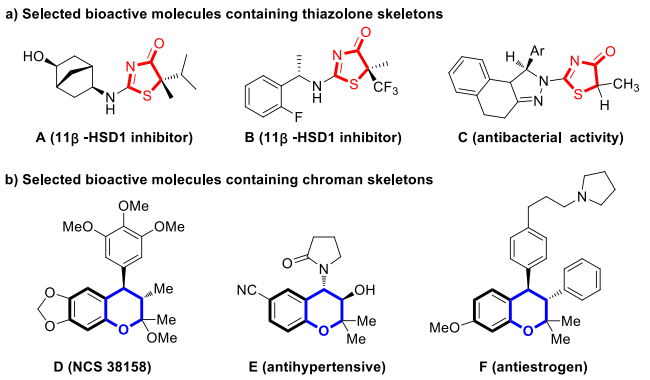

Figure 1. Representative bioactive molecules containing either thiazolone or chroman units.

one of the most attractive and straightforward way to construct such structural motifs in highly stereoselective form. Generally, 5-alkenyl thiazolones can act as either C2-synthons or C4-synthons for annulation reactions. Recently, many impressive examples on [4 + n] annulation of 5-alkenyl thiazolones have been achieved by the research groups of Wang,[6a] Ye,[6b] Guo,[6c] Li[6d] and others[6e-g] to construct diverse chiral thiazo-fused cyclic compounds (Scheme 1a, path A). Of note, almost all of reported examples focused on utilizing 5-alkenyl thiazolones as C4-syntons, and thus provided chiral thiazo-fused cycles. In sharp contrast, there is virtually very few

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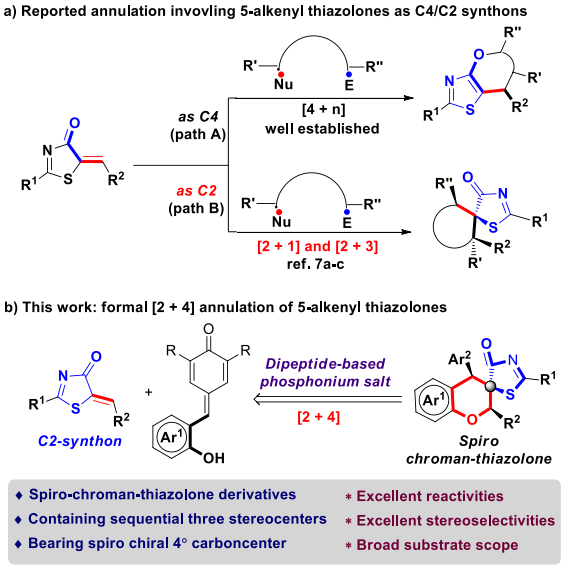
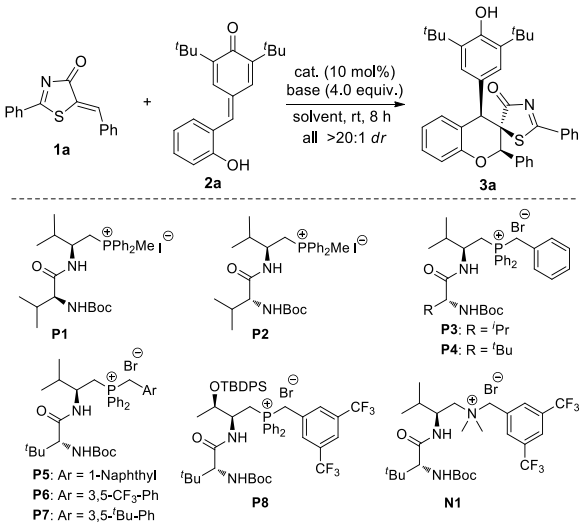


Scheme 1. Catalytic asymmetric annulation reactions of 5-alkenyl thiazolones.

progress on the use of such 5-alkenyl thiazolones as C2-synthons for annulations (Scheme 1a, path B), despite the fact that this type of reaction can be synthetically highly valuable. To the best of our knowledge, there have only three reports by Wang,[7a] Du[7b] and Yan[7c] group, respectively, which described that the 5-alkenyl thiazolones were used as C2-synthons for either [2 + 1] or [2 + 3] annulation. However, other examples on enantioselective formal [2 + n] type annulations with employing 5-alkenyl thiazolones as C2-substrates are not available so far.[7d] The difficulty in achieving an adequate level of stereochemical control in such [2 + n] reactions of 5-alkenyl thiazolones may be attributed to the fact that the newly formed spiro tetrasubstituted carbon stereocenter is rather steric hindrance. It thus became our goal to demonstrate whether the excellent stereochemical control can be realized or not in a bifunctional phosphonium salt promoted formal [2 + 4] annulation via employing 5-alkenyl thiazolones as C2-synthons.

Over the past decades, amino acid-derived phosphine catalysis has already been well established and widely applied in asymmetric synthesis.[8] Accordingly, the corresponding amino acid-derived phosphonium salt catalysis were recently developed by Zhao[9] and Lu.[10] Such bifunctional phosphonium salt catalysts contain both ion-pairing moiety and H-bonding active site,[11] which can be advantageous for asymmetric induction. Very recently, we developed a new type of dipeptide-based bifunctional phosphonium salts and successfully demonstrated their applications in asymmetric synthesis of structurally dense *tetra*-substituted aziridines[12a] and some other important heterocycles.[12b-d] On the other hand, we noted that chroman skeletons are prominent heterocyclic frameworks and widely distributed in many biologically active molecules and natural products with notable examples such as compound **D**,

Table 1. Optimization of reaction conditions[a]



entry	cat.	solvent	base	yield (%)[b]	ee[c]
1	**P1**	hexane	Cs_2CO_3	88	62
2	**P2**	hexane	Cs_2CO_3	90	67
3	**P3**	hexane	Cs_2CO_3	94	79
4	**P4**	hexane	Cs_2CO_3	91	88
5	**P5**	hexane	Cs_2CO_3	93	92
6	**P6**	hexane	Cs_2CO_3	94	93
7	**P7**	hexane	Cs_2CO_3	92	92
8	**P8**	hexane	Cs_2CO_3	92	91
9	**N1**	hexane	Cs_2CO_3	87	71
10	**P6**	PE	$K_3PO_4{\cdot}7H_2O$	97	>99
11[d]	**P6**	PE	$K_3PO_4{\cdot}7H_2O$	97	>99

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), catalyst (10 mol%) and base (4.0 equiv.) in the solvent (1.0 mL) at room temperature for 8 h. All *dr* values were determined by ^{1}H NMR of crude product. [b]Isolated yields. [c]The ee value was determined by chiral HPLC. [d]The reaction run with 5 mol% catalyst for 12 h. PE = petroleum ether (b.p. 60-90 °C).

antihypertensive activator **E** and estrogen receptor **F** (Figure 1b).[13,14] Recently, some [4 + 2] examples by employing hydroxyl-substituted *para*-quinone methides (*p*-QMs) as C4-synthons have been established,[15] and thus afforded various chiral chroman molecules. In this context, we envisioned that our dipeptide-based bifunctional phosphonium salts, which actually possess remarkably high tunability and structurally diversity, may guide 5-alkenyl thiazolone as a C2-synthon to accomplish formal [2 + 4] annulation with hydroxyl-substituted *p*-QMs for offering structurally spiro chroman-thiazolone molecules (Figure 1b). Herein, we describe the first highly enantioselective formal [2 + 4] annulation of 5-alkenyl thiazolones with *p*-QMs mediated by dipeptide-based bifunctional phosphonium salt catalysts, providing a facile and novel way to prepare functionalized spiro-chroman-thiazolone skeletons bearing three contiguous stereocenters.

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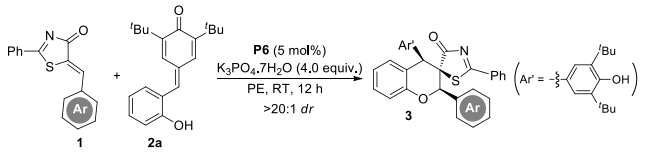
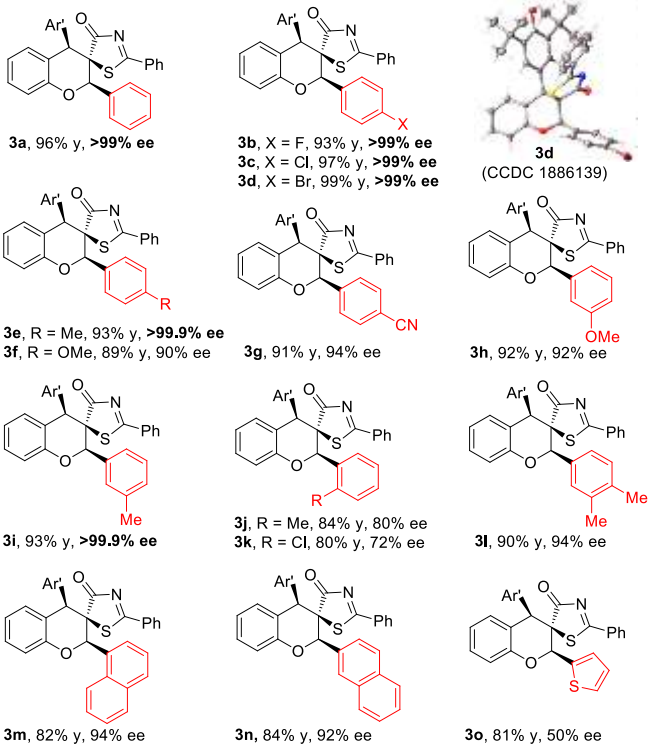
We began our studies by testing this reaction between 5-alkenyl thiazolone **1a** and *p*-QM **2a** with the bifunctional dipeptide phosphonium salt catalysts in the presence of Cs_2CO_3 and hexane at room temperature. To our delight, all the dipeptide-based phosphonium salts examined were effective in promoting this reaction to accomplish [2 + 4] annulations (Table 1, entries 1-8). While phosphonium iodides (**P1** and **P2**) were used, the desired annulation product was isolated in good yields and moderate ee values (entries 1 and 2). Encouraged by these initial results, we next prepared different dipeptide-based phosphonium bromides (**P3**–**P8**) and tested their catalytic reactivities. Generally, all tested dipeptide phosphonium bromides were found to be much effective in promoting this reaction for affording the cyclization products with excellent reactivity in good asymmetric induction (entries 3-8), and the catalyst P6 turned out to be the best with affording the cyclization product in 94% yield and 93% ee at room temperature. Notably, dipeptide-based ammonium salt catalyst N1 also can promote this reaction, but led to the desired product in slightly lower yield and enantioselectivity (entry 9). At last, quick screening of bases and solvents[16] identified that the petroleum ether (PE) was the solvent of choice and the $K_3PO_4.7H_2O$ was the suitable base (entry 10). Indeed, only 5 mol% catalyst was also sufficient to promote this reaction, and the corresponding product was isolated in 97% yield with >99% ee (entry 11).

With optimized reaction conditions in hand, the substrate scope for formal [2 + 4] annulation between 5-alkenyl thiazolones and hydroxyl-substituted *p*-QMs was explored. In general, various 5-alkenyl thiazolones bearing electron-neutral, -donating, or -withdrawing groups on the phenyl ring could be well employed (Table 2), furnishing the corresponding products **3** in high yields (up to 99%) with excellent both diastereo- and enantioselectivities (up to >20:1 dr and >99.9% ee). Specifically, the 5-alkenyl thiazolones bearing either electron-neutral or halogenated substitutents at the *para*-position of phenyl ring were perfectly compatible with the reaction conditions, affording the desired products **3a**–**d** in high yields (93–99%) with excellent diastereo- and enantioselectivities (>20:1 *dr*, all >99% ee). Substrates bearing both electron-donating and electron-withdrawing group at either *para*- or *meta*-position of the phenol ring also proved to be excellent substrates and afforded the corresponding products (**3e**–**i**) in high yields and excellent stereoselectivities. Notably, 5-alkenyl thiazolones containing substitutents at the *ortho*-position on the phenyl ring slightly lowered the enantioselectivities of the reaction (**3j** and **3k**), mainly due to the steric hindrance. Additionally, naphthyl-substituted thiazolones also were suitable substrates and afforded the products **3m** and **3n** with high ee values as 94% and 92%, respectively. Of note, thienyl-substituted thiazolone could work well to give the desired product in 81% yield but with moderate ee value (**3o**). The absolute configurations of the annulation products were assigned based on the X-ray crystal structural analysis of **3d**.[17]

Table 2. Scope for 5-alkenyl thiazolones[a]





[a]Reactions were performed with **1** (0.1 mmol), **2a** (0.12 mmol), $K_3PO_4.7H_2O$ (0.40 mmol) and the catalyst **P6** (5 mol%) in PE (2.0 mL) at room temperature for 12 h. Isolated yields provided and ee values were determined by chiral HPLC. PE = petroleum ether (b.p. 60-90 °C).

Encouraged by these results, the scope of *p*-QMs for this annulation process was further investigated. Delightedly, the annulation between 5-alkenyl thiazolone **1a** and *p*-QMs **2** proceeded smoothly with affording the desirable spiro products in the presence of dipeptide-based phosphonium **P6** under the fore-mentioned optimal conditions. As shown in Table 3, the reaction was applicable to various hydroxyl-substituted *p*-QMs bearing different aromatic rings, regardless of the positions and electronic properties of the substituents on the aromatic moiety, producing the expected spiro-chroman-thiazolones **4** in high yields (up to 95%) with excellent stereo selectivities (up to >20:1 *dr* and >99% ee). Moreover, the naphthyl *p*-QM was also found to be suitable substrate with affording the product **4l** in acceptable results. Furthermore, to verify the utility and practicality of this catalytic asymmetric [2 + 4] annulation reaction, the scaled-up synthetic reaction between 5-alkenyl thiazolone **1c** and *p*-QM **2a** was conducted under the optimal reaction conditions, and the product **3c** was isolated in high yield without any loss of

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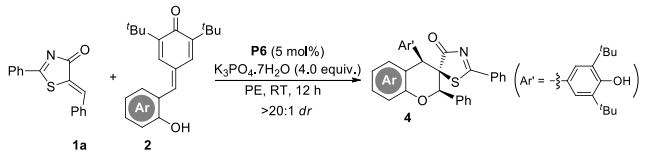
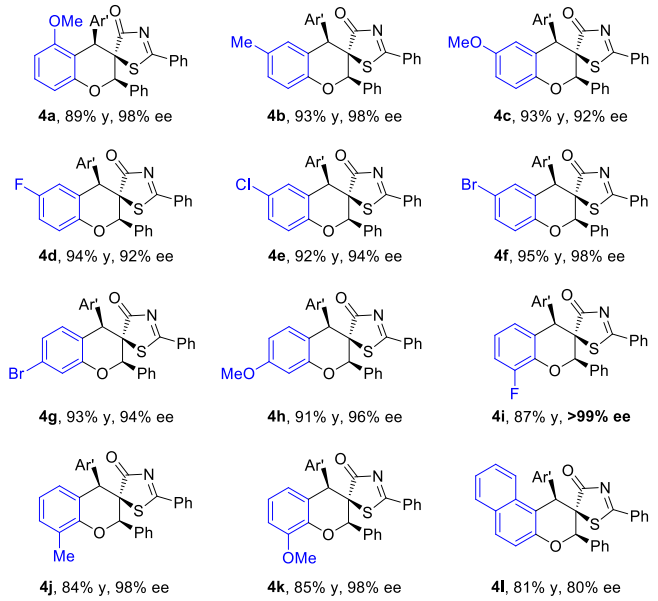
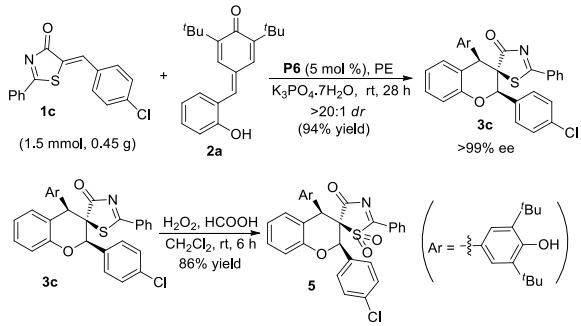
stereoselectivities. Furthermore, under oxidative conditions, the product **3c** was transferred into a chiral sulfone-containing coumpond **5** (Scheme 2).[18]

Table 3. Scope for *p*-QMs[a]





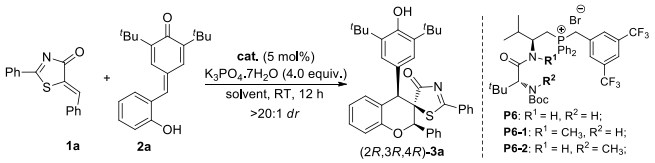
[a]Reactions were performed with **1a** (0.1 mmol), **2** (0.12 mmol), $K_3PO_4.7H_2O$ (0.40 mmol) and the catalyst **P6** (5 mol%) in PE (2.0 mL) at room temperature for 12 h. Isolated yields provided and ee were determined by chiral HPLC. PE = petroleum ether (b.p. 60-90 °C).



Scheme 2. Scale-up synthesis and synthetic elaboration of product.

Subsequently, we preformed further experiments to gain a better understanding of the reaction mechanism. As shown in Table 4, the methylated catalysts **P6-1** and **P6-2** were prepared and tested for the model reaction. When methylated phosphonium salts were used, the enantioselectivities decreased obviously (entries 1–3). Of note, when the reaction was performed in methanol, the enantioselectivity also dropped dramatically (entry 4). Thus, these preliminary results indicated the importance of both H-bonding and ion-pair interactions in this system. According to these results and our previous studies,[12] the plausible transition state models for the formation of major isomer were proposed (Figure 2). The high enantioselectivity mainly originates from the hydrogen-bonding and ion-pair interactions between the dipeptide-based phosphonium catalyst and generated phenolate anion (**TS1** and **TS2**).[19]

Table 4. Asymmetric formal [2 + 4] annulation promoted by different phosphonium salts and the proposed transition state models[a]



entry	cat.	solvent	T (°C)	t (h)	yield(%)[b]	ee[c]
1	**P6**	PE	rt	12	97	>99
2	**P6-1**	PE	rt	12	91	4
3	**P6-2**	PE	rt	12	90	51
4	**P6**	MeOH	rt	12	75	7

[a]Reactions were performed with **1a** (0.05 mmol), **2a** (0.06 mmol), base (0.20 mmol) and the catalyst (5 mol%) in the solvent (1.0 mL). [b]Isolated yields. [c]The ee values were determined by chiral HPLC.

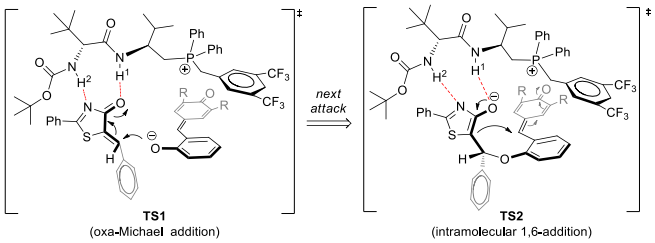


Figure 2. Proposed transition state models.

In summary, we have disclosed the first highly enantioselective formal [2 + 4] annulation of 5-alkenyl thiazolones with hydroxyl-substituted *p*-QMs by employing a dipeptide-based phosphonium salt as phase transfer catalyst. A series of optically pure and highly functionalized spiro-chroman-thiazolone molecules bearing three contiguous stereocenters were readily obtained with good isolated yields, excellent diastereoselectivities and enantioselectivities under mild reaction conditions. Moreover, the practicality and utility of this protocol were demonstrated by the scale-up synthesis and facile elaboration of product. Detailed mechanistic investigations and applications of this novel phosphonium salt catalysis to other challenging asymmetric synthesis are currently ongoing in our laboratory.

Experimental Section

General Procedure for [2 + 4] Annulation

To a dried round bottle flask with a magnetic stirring bar were added 5-alkenyl thiazolone **1** (0.1 mmol) and *para*-quinone methide **2** (0.12 mmol), then $K_3PO_4.7H_2O$ (0.40 mmol) and catalyst **P6** (5 mol%) was added followed by the addition of petroleum ether (2.0 mL). The reaction mixture was stirred at rt for 12 h, and TLC show that the rection was completed. Then, The mixture was directly purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to afford desired spiro-chroman-thiazolone **3** as white solid.

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[16] See either Table S2 or Table S3 in SI for more details.

[17] CCDC 1886139 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[18] See Scheme S2 in SI for more details.

[19] See Figure S1 in SI for proposed reaction cycle.

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Enantioselective Construction of Spiro[chroman-thiazolones]: Bifunctional Phosphonium Salt-Catalyzed [2 + 4] Annulation between 5-Alkenyl Thiazolones and *ortho*-Hydroxyphenyl-Substituted *para*-Quinone Methides

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