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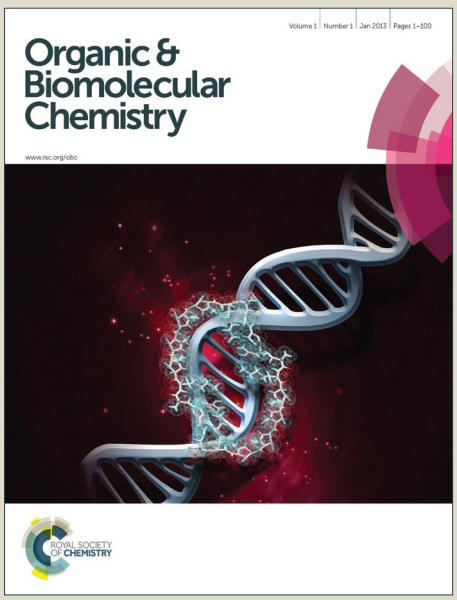

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The first catalytic asymmetric thioacetalization by chiral phosphoric acid catalysis

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We report here the first catalytic asymmetric thioacetalization of salicylaldehyde and dithiol. Chiral phosphoric acid *STRIP* C5 is identified as a powerful catalyst for this reaction to afford various chiral dithioacetals in high to excellent yield and enantioselectivity under mild condition.

Chiral sulfur-containing compounds are widely present in bioactive natural products and synthetic pharmaceuticals.[1] In addition, they could also serve as building blocks for chiral ligands and auxiliaries as well as synthetic intermediates in natural product synthesis.[2] Therefore, considerable efforts have been devoted to the catalytic enantioselective synthesis of optically active sulfur-containing compounds.[3] Despite significant processes, very few attention has been paid to the enantioselective synthesis of chiral dithioacetal/ketals. Notably, apart from their synthetic applications,[4] dithioacetal/ketal functionality could be used to modulate properties of bioactive compounds (Figure 1).[5] For example, UCSF8, dithioketal derivative of haloperidol, showed an improved inhibition constant K_i for HIV-1 protease, and better selectivity for HIV-1 protease over pepsin (more than 40 fold). [5a] The incorporation of a dithioketal moiety into enalapril, the first nonmercaptan angiotensin converting enzyme inhibitor for treatment of hypertension, gave potent inhibitor spirapril.[5b]

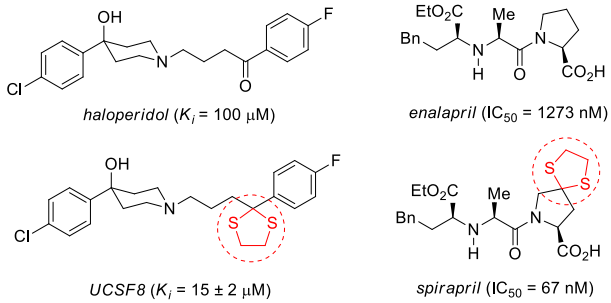
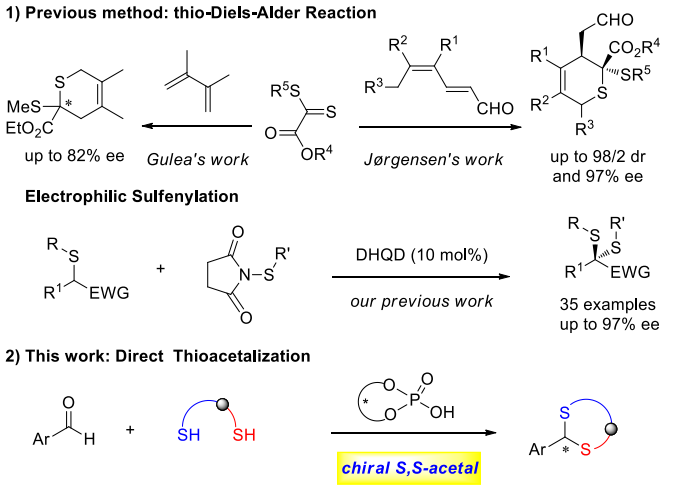


Figure 1. Dithioketal-containing bioactive compounds.

Considering the importance of chirality in medicinal research to enhance drug efficacy and specificity,[6] the introduction of a chiral dithioacetal/ketal moiety for structure-activity relationship studies is rewarding. Therefore, the development of catalytic asymmetric protocol for chiral dithioacetal/ketals is highly desirable.

To the best of our knowledge, the enantioselective synthesis of chiral dithioacetals has never been realized, though there have been three reports concerning the catalytic asymmetric synthesis of chiral dithioketals (Scheme 1).[7] In 2010, Gulea et al pioneered thio-Diels-Alder reaction of dithioesters with dienes by using chiral Cu(II) as the catalyst.[7a] Subsequently, Jørgensen accomplished an efficient asymmetric cycloaddition of dithioesters and unsaturated enals via trienamine catalysis, affording the chiral dithioketals in high yield and selectivity.[7b] We recently reported a chiral Brønsted base catalyzed asymmetric sulfenylation of *S*-based active methine compounds, which enabled the synthesis of chiral dithioketals in rich structural diversity.[7c] With our continuing interests in catalytic asymmetric synthesis of chiral *S*-containing compounds,[8] we wish to report here the first chiral phosphoric acid catalyzed asymmetric thioacetalization of aldehydes to optically active dithioacetals.



Scheme 1. Strategies to optically active dithioketal and dithioacetal.

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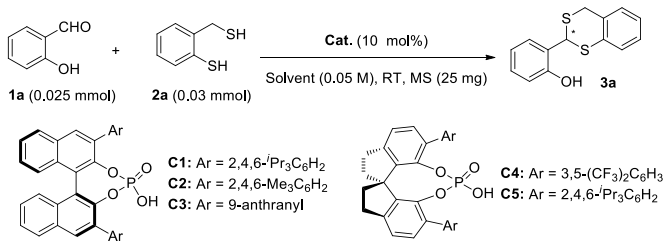
Since the pioneering work of Akiyama and Terada,[9] chiral phosphoric acid catalysis has been established as a powerful strategy for many important enantioselective transformations.[10] Based on the well-established ability for the activation of imines, chiral phosphoric acid catalyzed asymmetric synthesis of *N*,*N*-, *N*,*O*-, *N*,*S*- and *N*,*Se*-acetal had been well studied by the group of Antilla,[11] List,[12] Rueping[13] and others.[14] Subsequently, List et al made a breakthrough in this area, who realized the enantioselective synthesis of chiral *O*,*O*-acetal via the chiral phosphoric acid catalyzed transacetalization,[15] which is very challenging due to weak and indiscriminate binging between the critical oxocarbenium ion intermediate and the chiral anion.[16] Afterward, the same group realized the asymmetric catalytic spiroacetalization[17a] and acetalization[17b,c] of aldehyde by using novel confined Brønsted acid, generating chiral *O*,*O*-acetal with high enantioselectivity.[18]

Encouraged by these pioneering works, along with the fact that the enantioselective thioacetalization, most direct path to chiral *S*,*S*-acetals, has never been realized, we thus envisage to investigate the synthesis of chiral *S*,*S*-acetal via the asymmetric thioacetalization of aldehyde by chiral phosphoric acid catalysis.

Table 1. Reaction optimization

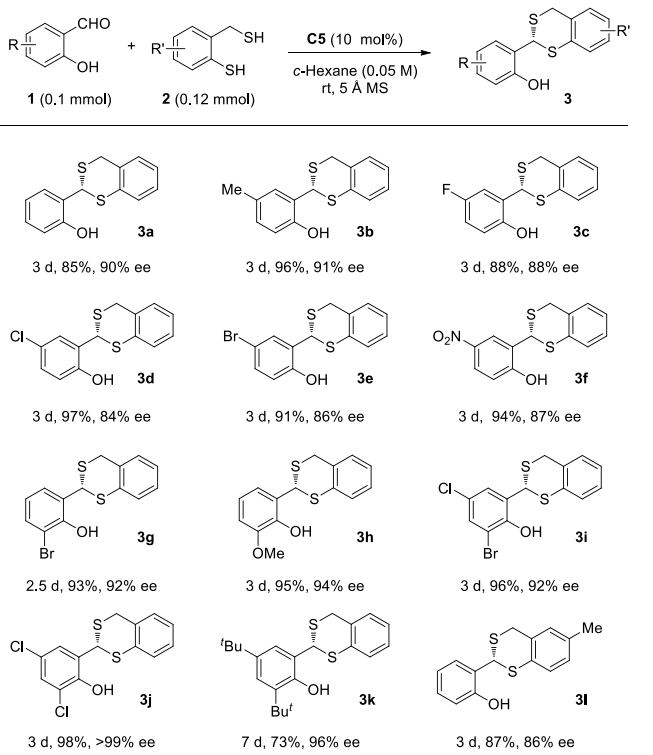


Entry	Cat.	Solvent	MS	Time (h)	Conv. (%)[a]	Ee[b]
1	**C1**	*c*-Hexane	5 Å	65	27	-54
2	**C2**	*c*-Hexane	5 Å	65	62	-31
3	**C3**	*c*-Hexane	5 Å	12	96	-25
4	**C4**	*c*-Hexane	5 Å	65	90	33
5	**C5**	*c*-Hexane	5 Å	65	80	91
6[c]	**C5**	*c*-Hexane	5 Å	40	80	88
7[c]	**C5**	*n*-Hexane	5 Å	65	61	82
8[c]	**C5**	Toluene	5 Å	65	44	91
9[c]	**C5**	*c*-Hexane	3 Å	40	40	91
10[c]	**C5**	*c*-Hexane	4 Å	40	20	92
11[c]	**C5**	*c*-Hexane	13 X	40	32	92
12	**C5**	*c*-Hexane	---	65	34	88
13[d]	**C5**	*c*-Hexane	5 Å	72	85	90

[a] Determined by GC-MS analysis. [b] Determined by chiral HPLC analysis. [c] 0.1 M. [d] On a 0.1 mmol scale, isolated yield.

Initially, we investigated the reaction of salicylaldehyde **1a** and dithiol **2a**, at ambient temperature in *c*-hexane with 5Å molecular sieve (MS) as additive. Chiral BINOL-derived phosphoric acids with different 3,3'-substituents were firstly examined. Preliminary study revealed that chiral phosphoric acid *TRIP* **C1** could catalyze the asymmetric thioacetalization smoothly to afford the desired *S*,*S*-acetal **3a** in 54% ee, with 27% conversion after 65 h (Table 1, entry 1). The use of catalyst **C2** led to a decreased enantioselectivity (entry 2). Changing the substituent to 9-anthranyl, **C3** led to significant increase in the reactivity, 96% conversion could be achieved after only 12 hours, but the ee value decreased to 25% (entry 3). It is well known that the skeleton of chiral phosphoric acids have a significant influence on their performance. With this in mind, chiral phosphoric acids with 1,1'-spirobiindane backbone were investigated subsequently.[19,20] It was found that **C4** could catalyze the reaction to give product **3a** in 33% ee, with 90% conversion (entry 4). To our delight, the phosphoric acid *STRIP* **C5**, which was previously used by List et al in the asymmetric transacetalization,[15b] enabled a highly asymmetric reaction affording **3a** in 91% ee, albeit with a slightly decreased reactivity (entry 5). Increasing the substrate concentration from 0.05 M to 0.1 M, the conversion could be improved, but the ee value dropped to 88% (entry 6). Solvent effect revealed that *c*-hexane was superior to other solvents, such as *n*-hexane and toluene (entry 6 vs entries 7-8). Although a slightly higher ee value could be obtained in toluene, the reaction was very slow, as only 44% conversion could be obtained after 65 hours (entry 8). Further investigation revealed that MS additive had a great influence on reaction rate, and 5Å MS gave the best result (entries 9-12). Ultimately, prolonging reaction time to 72 hours, product **3a** could be obtained in 85% yield and 90% ee in the presence of 10 mol% **C5** and 5Å MS (entry 13).

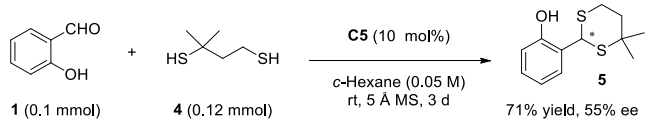
Table 2 Reaction Scope[a-b]



[a] Isolated yield. [b] Determined by HPLC analysis.

With the optimized reaction condition in hand, the substrate scope with respected to aldehyde **1** was firstly examined (Table 2). Generally, a series of commercial available salicylaldehydes worked well, affording the desired chiral thioacetal **3** in high to excellent yields and ee values. The substituents on the phenyl ring of salicylaldehyde **1** had a little influence on the enantioselectivity. For instance, aldehyde containing a 5-methyl group could furnish **3b** in 96% yield and 91% ee, but the ee values decreased slightly with electron-withdrawing group (**3c**-**3f**, 84-88% ee). Aldehydes with both bromide and methoxyl group at C3 position were all viable, giving the corresponding products **3g** and **3h** in excellent yields and enantioselectivies.

Furthermore, 3,5-disubstituted products **3i**-**3k** could also be obtained in excellent enantioselectivies. Due to the low reactivity of 3,5-di-*tert*-butyl salicylaldehyde, seven days was required for full conversion giving product **3k** in 73% yield. Subsequently, the dithiol bearing a 4-methyl group on the aromatic ring was investigated, and the corresponding dithioacetal **3l** could be obtained in 87% yield with 86% ee. We also explored the application of this catalyst system to aliphatic 1,3-dithiol **4**, while only moderate enantioselectivity was obtained, which indicated that the rigid phenyl ring structure of dithiol might be important for achieving high ee value.



Scheme 2. Asymmetric thioacetalization with aliphatic 1,3-dithiol.

The absolute configuration of chiral dithioacetal **3g** was unambiguously determined to be *R* by the single-crystal X-ray analysis (Figure 2). The configuration of other products **3** was tentatively assigned by analogy.

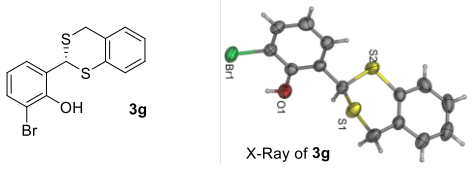
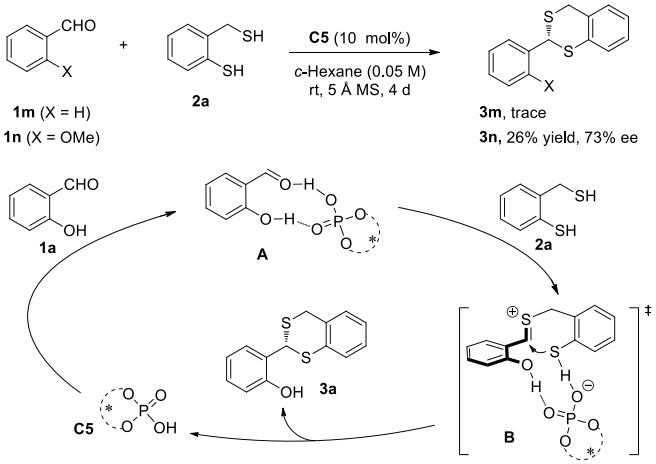


Figure 2. Single-crystal X-ray structure of product **3g**.

Control experiments revealed that the free hydroxyl group of aldehyde was very critical for the successful of this phosphoric acid catalyzed asymmetric thioacetalization, as only trace amount of **3m** could be detected when using benzaldehyde **1m** without hydroxyl group, and only 26% yield with 73% ee values was obtained in case of *o*-methoxylbenzaldehyde **1n** (Scheme 3). The same phenomenon had also been observed by List et al in the chiral Brønsted acid catalyzed asymmetric Prins cyclization.[21a] It was believed that the hydrogen bond between chiral catalyst and the free hydroxyl moiety of salicylaldehyde had a significant contribution for high reactivity and stereoselectivity control.[21]



Scheme 3. Control experiments and proposed mechanism.

Based on these observations, a possible reaction mechanism was proposed in Scheme 3. Initially, the hydrogen bonding among chiral phosphoric acid **C5**, hydroxyl and carbonyl group facilitated the addition of the primary thiol moiety of the dithiol **1a** to the activated aldehyde.[17b] After the expulsion of a water molecular, the critical thiocarbenium ion **B** was formed, in which the generated hydrogen bonds among chiral acid, hydroxyl and thiophenol group directed the nucleophilic attack of the thiophenol moiety from *Re* face of the thiocarbenium ion, affording *R*-configured product and releasing the chiral catalyst.

In summary, we have developed the first catalytic asymmetric thioacetalization of salicylaldehyde and dithiol. Chiral phosphoric acid *STRIP* was identified as a powerful catalyst for this reaction and various chiral dithioacetals could be achieved in high to excellent yield and enantioselectivity under mild condition. Further studies into the reaction mechanism, synthetic application and the development of new reactions to optically active dithioacetal/ketals are now in progress in our laboratory.

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Notes and references

CCDC 1413673 (**3g**) contain the supplementary crystallographic data for this paper.

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