

# Carbene-Catalyzed Access to Thiochromene Derivatives: Control of Reaction Pathways via Slow Release of Thiols from Disulfides

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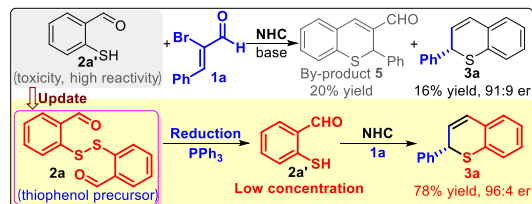
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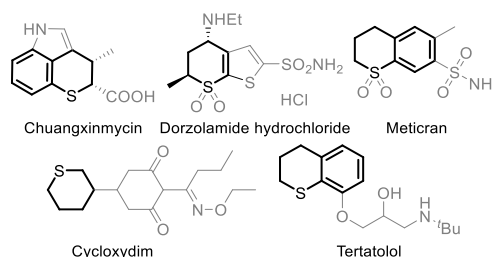
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Supporting Information Placeholder



**ABSTRACT:** The substrates containing disulfide bonds, which are more stable and less smelling, could be used as thiophenol precursors in organic synthesis. Herein, a N-heterocyclic carbene (NHC)-catalyzed reaction between  $\alpha$ -bromoaldehydes and 2,2'-dithiodibenzaldehydes was developed. Through the sustained release strategy, the side reaction can be effectively inhibited, and the chiral thiochromene derivatives can be obtained with good yields and high optical purities. Application studies showed encouraging results when the desired products were explored for antimicrobial utilities in pesticide development.

Sulfur-containing heterocyclic compounds, such as thiochromenes, thiochromanes and their derivatives, are widely found in drugs, pesticides and natural products<sup>1</sup> (Figure 1). For example, Chuangxinmycin is a natural active molecule which is isolated from the actinomycetes *Actinoplanes tsinanensis*.<sup>2</sup> It showed broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria *in vitro*. Tertatolol is a prescription drug for the treatment of hypertension and hypertension with renal insufficiency.<sup>3</sup> Cycloxydim is a selective post seedling herbicide<sup>4</sup>, which is used to control annual and perennial gramineous weeds in broadleaf crop fields. Therefore, methods for preparing sulfur-containing molecules continue to receive considerable attentions.<sup>5</sup> One of such methods is to start with thiols (including thiophenols) to make molecules with additional complexities. In recent decades, organic catalysts have been used to mediate this type of reactions involving thiols.<sup>6</sup> Despite of the impressive progress, two important challenges remain to be addressed: bad smelling and toxicity of the thiol molecules, and high reactivity of thiols

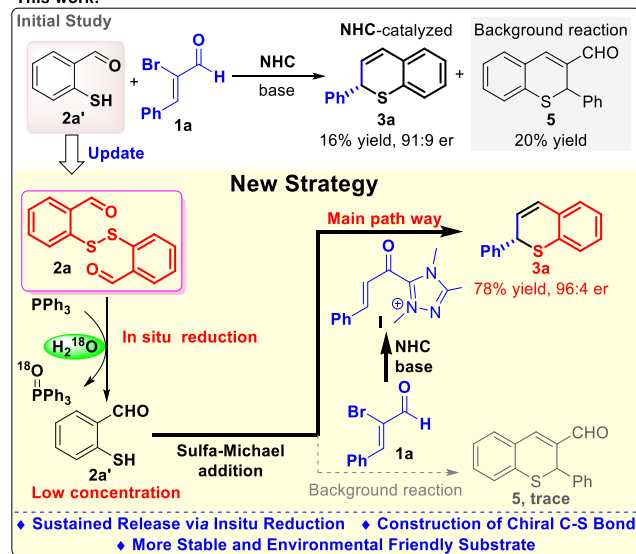


**Figure 1.** Thiochromene derivatives bioactive molecules.

that leads to multiple side reactions.<sup>7</sup> It is well known that thiols can be oxidized to disulfides, and disulfides can be readily reduced back to thiols under various conditions.<sup>8</sup> Typically, disulfides are more stable and less volatile (and less smelling), and thus can be used as thiol precursors in organic synthesis.<sup>9</sup> Here we report a carbene-catalyzed<sup>10</sup> construction of thiochromene derivatives by using disulfide as thiophenol precursor. With a slow release of thiophenol from the

corresponding disulfide under the assistance of triphenylphosphine (PPh<sub>3</sub>) and water, undesired side reactions (non-catalytic background reactions) can be avoided.

This work:



**Figure 2.** Asymmetric access to chiral sulfur containing heterocycles.

Our key findings are summarized in Figure 2. When thiophenol **2a'** was employed as nucleophile to react with bromoenal<sup>11</sup> **1a** under the catalysis of pre-NHC **A**, the desired product **3a** was isolated with 16% yield and 91:9 er while the by-product **5** was isolated with 20% yield. It suggested that the substrate **2a'** can directly react with **1a** when **2a'** was kept at a high concentration. Inspired by the results, the background reaction may be inhibited by decreasing the concentration of thiophenol. Thus, 2,2'-dithiodibenzaldehyde **2a** was selected as thiophenol precursor, the sulfur anion could not be spontaneously generated from the disulfide bond without reductant. PPh<sub>3</sub> can be used to reduce the disulfide bond to insitu generate the sulfur anion, which can decrease the concentration of **2a'**.<sup>12</sup> Then, the sulfur anion with low concentration reacted with acyl azolium intermediate (**I**), and further reactions were carried out to obtain the chiral thiochromene **3a** with 78% yield and 96:4 er.

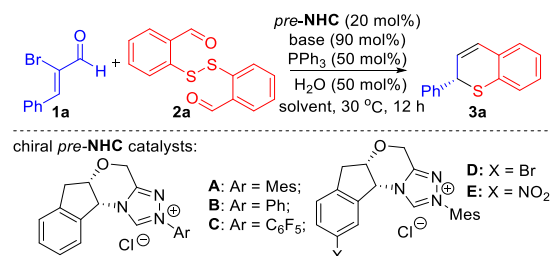
**Table 1.** The effect of water addition for model reaction<sup>a</sup>

Entry	Additive	Yield(%) <sup>b</sup>	Er <sup>c</sup>
1	no additive	35	95:5
2	4 Å MS (150mg)	16	97:3
3	H <sub>2</sub> O (0.025 mmol)	39	94:6
4	H <sub>2</sub> O (0.050 mmol)	67	92:8
5	H <sub>2</sub> O (0.100 mmol)	70	88:12

<sup>a</sup>Unless otherwise specified, the reactions were carried under N<sub>2</sub> atmosphere using **1a** (0.12 mmol), **2a** (0.05 mmol), PPh<sub>3</sub> (0.05 mmol), pre-NHC **A** (0.02 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.09 mmol) and THF (2.0 mL) at 30 °C for 12 h. <sup>b</sup>Isolated yield of **3a**. <sup>c</sup>The er values of **3a** were determined via HPLC on the chiral stationary phase.

2,2'-Dithiodibenzaldehyde **2a** was selected as the sulfur nucleophilic precursor to react with bromoenal **1a** under the NHC catalysis. Firstly, the desired product **3a** was obtained with excellent enantioselectivity and 35% yield with the using of aminoindanol-derived triazolium **A**<sup>13</sup> as the NHC precatalyst (Table 1, entry 1). After the addition of 4 Å molecular sieves (4 Å MS) (150 mg), the enantioselectivity was slightly improved, but the yield was obviously decreased to 16% (Table 1, entry 2). To our delight, the yield of **3a** was increased to 39% with preserved er value (Table 1, entry 3). It was found that the yield of **3a** was increased with the increasing of water, but the er value was obviously decreased to 88:12 (Table 1, entries 4 and 5). Therefore, the potential reaction condition (Table 1, entry 4) was used to further explore the optimal reaction conditions.

**Table 2.** Condition optimization<sup>a</sup>



Entry	Pre-NHC	Solvent	Base	Yield(%) <sup>b</sup>	Er <sup>c</sup>
1	<b>A</b>	THF	Cs <sub>2</sub> CO <sub>3</sub>	67	92:8
2	<b>B</b>	THF	Cs <sub>2</sub> CO <sub>3</sub>	<10	78:22
3	<b>C</b>	THF	Cs <sub>2</sub> CO <sub>3</sub>	<10	74:26
4	<b>D</b>	THF	Cs <sub>2</sub> CO <sub>3</sub>	70	94:6
5	<b>E</b>	THF	Cs <sub>2</sub> CO <sub>3</sub>	65	93:7
6	<b>D</b>	MeCN	Cs <sub>2</sub> CO <sub>3</sub>	13	92:8
7	<b>D</b>	Toluene	Cs <sub>2</sub> CO <sub>3</sub>	17	68:32
8	<b>D</b>	EA	Cs <sub>2</sub> CO <sub>3</sub>	63	90:10
9	<b>D</b>	THF	DBU	35	91:9
10	<b>D</b>	THF	Et <sub>3</sub> N	24	92:8
11	<b>D</b>	THF	K <sub>2</sub> CO <sub>3</sub>	78	96:4

<sup>a</sup>Unless otherwise specified, the reactions were carried under N<sub>2</sub> atmosphere using **1a** (0.12 mmol), **2a** (0.05 mmol), PPh<sub>3</sub> (0.05 mmol), pre-NHC (0.02 mmol), base (0.09 mmol), H<sub>2</sub>O (0.05 mmol) and solvent (2.0 mL) at 30 °C for 12 h.

<sup>b</sup>Isolated yield of **3a**. <sup>c</sup>The er values of **3a** were determined via HPLC on the chiral stationary phase.

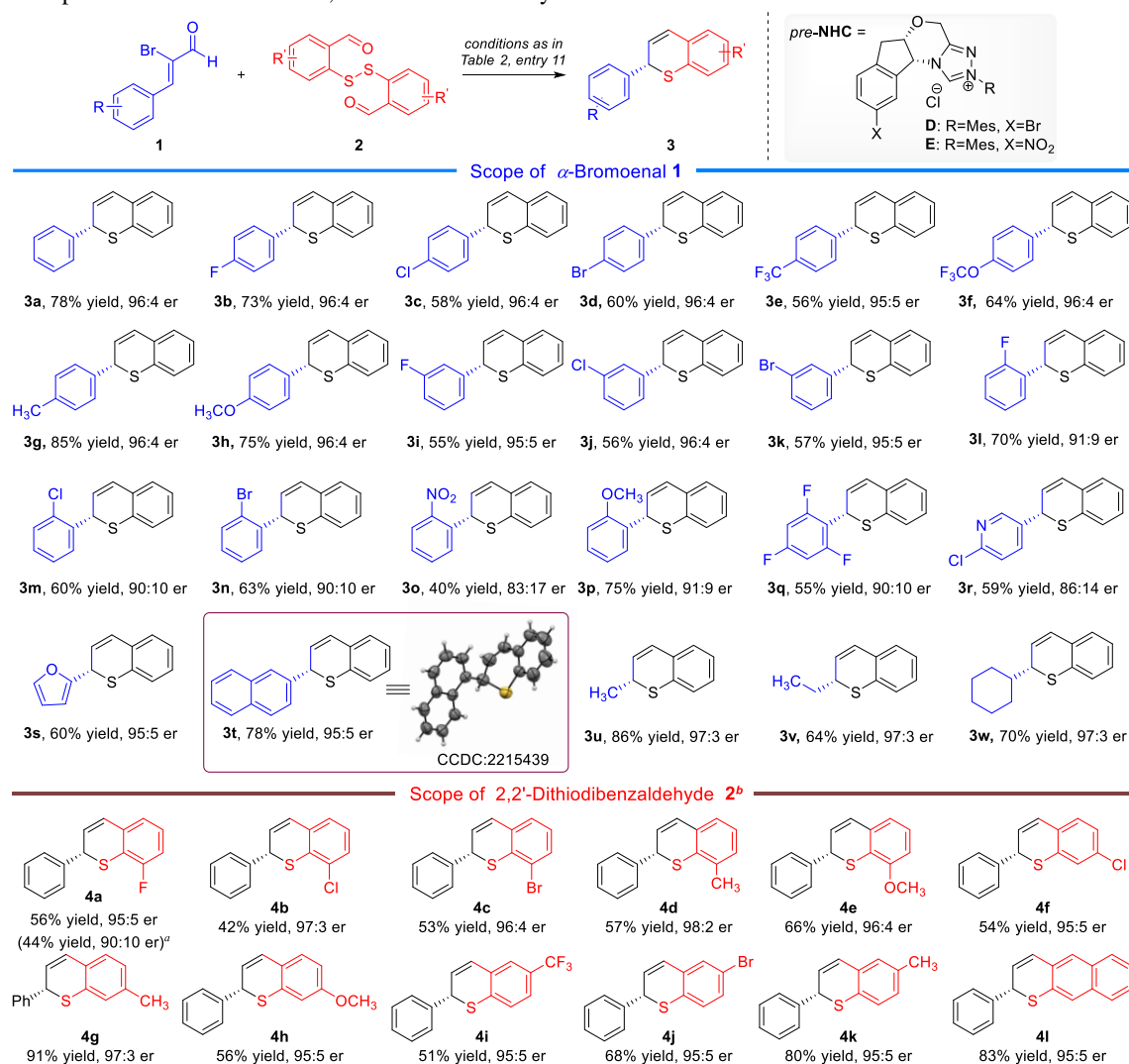
Furthermore, we optimized the reaction conditions in the presence of water. NHC catalysts<sup>14</sup> bearing N-Ph and N-C<sub>6</sub>F<sub>5</sub> group were not efficient for the reactions, which made the yield of **3a** decrease dramatically (low than 10%) (Table 2, entries 2 and 3). It was found that the pre-NHC **D**<sup>15</sup> bearing a bromo atom on the benzene ring gave the desired product **3a** with 70% yield and 94:6 er (Table 1, entry 4). Meanwhile, the pre-NHC **E**<sup>16</sup> was examined and the result was similar to pre-NHC **D**. Then, we used the pre-NHC **D** to exam the different solvents in this protocol. Switching the THF with MeCN, Toluene and EA, the unacceptable enantioselectivities and yields were obtained (Table 2, entries 6, 7 and 8). Finally, the bases were explored, it was found that the K<sub>2</sub>CO<sub>3</sub> gave excellent yield and enantioselectivity (Table 2, entries 9, 10 and 11).

With the optimized reaction condition in hand, the reaction scope of both bromoenals **1** and 2,2'-dithiodibenzaldehyde **2a** was examined (Scheme 1). Different substitution patterns of bromoenals **1** were explored. Substituents with electron-withdrawing groups (**3b-3f** and **3i-3k**) and electron-donating groups (**3g, 3h**) could be installed on the *para*- and *meta*-positions of benzene ring of bromoenals **1**, with the corresponding products afforded in moderate to good yields and excellent enantioselectivities. However, the installation of electron-withdrawing groups (**3l-3o**) and electron-donating groups (**3p**) at the *ortho*-position of the benzene ring of **1** led to moderate yields and decreased er values. The same result was also shown when the benzene ring of substrate **1** had multiple electron-withdrawing groups (**3q**). Changing the phenyl group of the bromoenal into heteroaryl group, the yields and enantioselectivities of the products were slightly dropped

(**3r, 3s**). The  $\beta$ -phenyl group of substrates **1** could be replaced with the naphthalene group, and the product was obtained in good yield and excellent enantioselectivity (**3t**). Aliphatic  $\alpha$ -bromoaldehydes could also be used as suitable reaction substrate in this reaction, with the desired products afforded in moderate to excellent yields and high optical purities (**3u-3w**).

When exploring the substituents tolerance on the benzene ring of 2,2'-dithiodibenzaldehydes **2**, the yields and enantioselectivities of most of the products were reduced under standard reaction conditions. To our delight, when changing *pre*-NHC **D** to *pre*-NHC **E** simply, substituents were also well tolerated on the benzene ring of the 2,2'-Dithiodibenzaldehyde **2**, with the desired products afforded in moderate to excellent yields and excellent er values regardless of their electronic properties and substitution patterns (**4a-4l**).

**Scheme 1.** Scope of  $\alpha$ -bromoenal **1** and 2,2'-dithiodibenzaldehyde **2**<sup>a</sup>



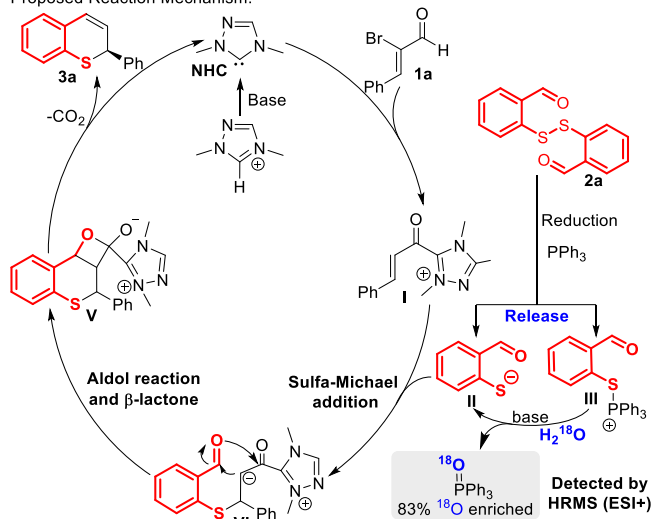
[a] Reaction conditions as stated in Table 2, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined *via* HPLC on chiral stationary phase. [b] *pre*-NHC **E** was used as catalyst for scope of 2,2'-dithiodibenzaldehyde **2**. Ellipsoid contour probability level = 50% (CCDC 2215439).

In the reaction, it was found that the water was played an important role in the pathway control. To understand the effects of the water in the reaction, additional experiments were

performed. <sup>18</sup>O-labeled water (98% <sup>18</sup>O labeled) was employed as additive to study the mechanism. Subsequently, the desired product **3a** and triphenylphosphine oxide (TPPO) were isolated,

and the TPPO was found with isotopic anomaly (83%  $^{18}\text{O}$  labeled) *via* high resolution mass spectroscopy (HRMS). The results suggested that the water participated in the reaction and the intermediate **III** can be hydrolyzed to form intermediate **II**. The result was similar to Corey-Nicolaou macrolactonization,<sup>17</sup> in which the  $\text{PPh}_3$  can be oxidized by the disulfide bond to form

Proposed Reaction Mechanism:



**Figure 3.** Proposed catalytic cycle.

TPPO. The concentration of intermediate **II** was significant to the reaction, and with the sustained release strategy, keeping the intermediate **II** at a low concentration can inhibit the by-product pathway. The addition of the sulfur atom from intermediate **II** to the  $\beta$ -carbon of intermediate **I** gave intermediate **IV** through the Thiol-Michael reaction, with a new carbon-sulfur bond formed in a highly enantioselective manner. Further reactions of **IV** (through intramolecular Aldol reaction and  $\beta$ -lactone formation) gave intermediate **V**, which undergoes decarboxylation to afford chiral thiochromene **3a**.

**Table 3.** *In vitro* inhibitive activities of the planar chiral compounds against *Xanthomonas axonopodis* pv. *citri* (*Xac*)<sup>a</sup>

Compounds	<i>Xac</i> inhibition rate (%)	
	100 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$
<b>3b</b>	75.86 $\pm$ 0.51	61.67 $\pm$ 0.49
<b>3d</b>	66.56 $\pm$ 0.85	59.68 $\pm$ 1.21
<b>3e</b>	67.85 $\pm$ 0.67	58.44 $\pm$ 0.25
<b>3f</b>	72.32 $\pm$ 2.13	57.68 $\pm$ 2.04
<b>3l</b>	66.38 $\pm$ 0.59	54.07 $\pm$ 1.65
<b>3n</b>	85.21 $\pm$ 0.72	51.24 $\pm$ 0.78
<b>3s</b>	77.83 $\pm$ 0.95	59.66 $\pm$ 0.49
<b>3t</b>	87.82 $\pm$ 0.63	62.84 $\pm$ 1.05
<b>3u</b>	65.54 $\pm$ 0.15	62.20 $\pm$ 2.27
<b>3w</b>	61.51 $\pm$ 0.87	41.24 $\pm$ 0.38
<b>4f</b>	72.71 $\pm$ 0.76	52.09 $\pm$ 0.23
<b>4g</b>	64.01 $\pm$ 1.36	49.55 $\pm$ 1.60
TC <sup>b</sup>	57.74 $\pm$ 0.82	30.51 $\pm$ 1.08

<sup>a</sup>All data were average data of three replicates. <sup>b</sup>TC = thiodiazole copper.

To our delight, the chiral thiochromene derivatives obtained from our method also exhibit interesting biological activities in the turbidimetric test at 100 and 50  $\mu\text{g/mL}$  of the *in vitro* antibacterial activity against *Xanthomonas axonopodis* pv. *citri* (*Xac*)<sup>18</sup> (Table 3). Compared with thiodiazole copper (TC) that has been widely used as commercially available antibacterial agriculturals, 12 of the chiral products obtained from our

method have shown obviously superior antibacterial activities and can be regarded as promising candidates in the search for new pesticide structures.

In summary, we have successfully obtained chiral thiochromene derivatives under NHC-catalyzed by controlling the reaction pathways *via* slow release of thiols from disulfides. The disulfide bond containing substrate was used as thiophenol precursor to react with corresponding acyl azolium intermediate. The background reaction can be inhibited by the slow release of thiophenol. Water has also been found to play a key role in the hydrolysis of thiosulfate and further slowly release thiophenol to participate in the reaction, which obviously improved the yield of the desired product. Further studies on the bioactivities of chiral thiochromene derivatives obtained from our method for agricultural applications had been evaluated, the preliminary results suggested that these molecules show encouraging *in vitro* activities against *Xac*. Our strategy in controlling reaction pathways *via* insitu sustained release can be further used in developing new reactions, especially those where effective concentration of the substrates matters.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

### Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interests.

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