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Asymmetric Catalytic Synthesis of Thiochromenes via an Acyl Transfer-Initiated Cascade

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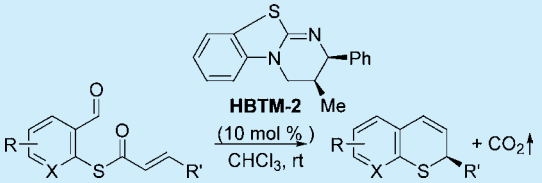
Supporting Information

ABSTRACT: A novel, reagent-free catalytic transformation of α,β-unsaturated thioesters into 2-substituted thiochromenes has been developed, with carbon dioxide as the only byproduct. Amidine-based catalysts, particularly homobenzotetramisole and its analogues, achieve high enantioselectivities and yields in this process.



Enantioselective synthesis of 2-substituted thiochromenes and thiochromans has attracted some attention because of the potential of their derivatives in drug design[1] (Figure 1).

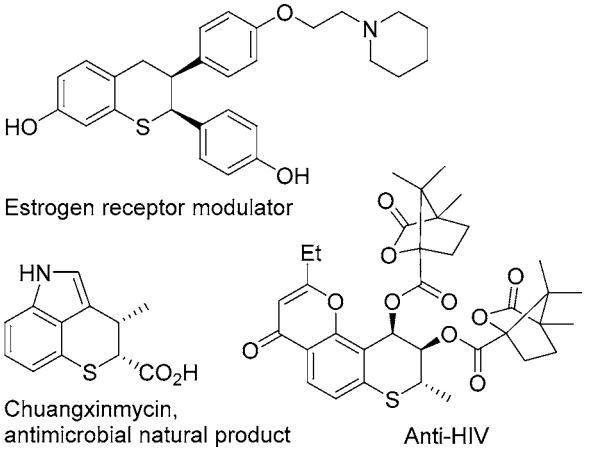


Figure 1. 2-Substituted thiochroman derivatives.

All existing asymmetric catalytic methods,[2] however, give rise to products bearing an electron-withdrawing substituent at C3 (Figure 2), which limits their application. In this communication, we report the first method enabling the synthesis of 3,4-unsubstituted chiral thiochromenes in a catalytic, highly enantioselective manner.

Our long-standing interest in developing amidine-based catalysts (ABCs) (Figure 3)[3] and their synthetic applications[4] has recently led us to explore their efficacy in activating thioesters via nucleophilic acyl substitution. Encouraged by our initial results, we turned our attention to α,β-unsaturated thioesters (**7**), which were envisioned to undergo the transformation of the initially generated ion pair **8** into zwitterionic enolate **9**, a potential precursor to a variety of formal cycloadditions (cf. **9** → **10**).[5] In a sense, the conversion of **7** into **9** might be viewed as a conceptual

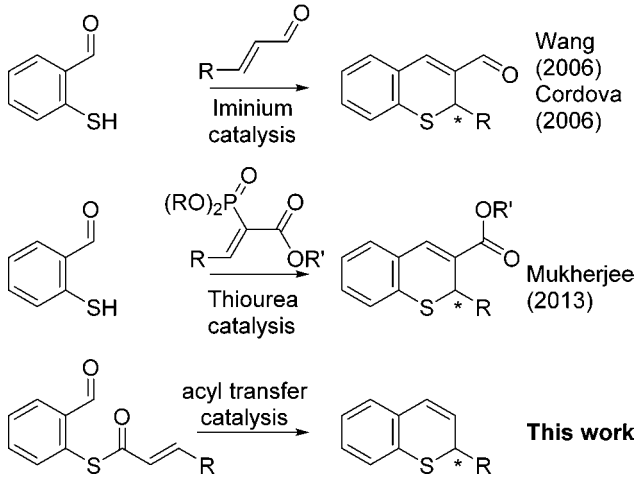


Figure 2. Asymmetric approaches to thiochromenes.

equivalent of its 1,3-rearrangement into the hypothetical β-sulfenylketene **11** (Scheme 1).[6]

With this in mind, we prepared thioester **12a** bearing an adjacent aldehyde group intended to serve as a trap for the putative zwitterionic enolate. To our satisfaction, this test substrate underwent clean conversion into 2-phenylthiochromene (**13a**) in 94% yield in the presence of DHPB (**5**)[7] (Scheme 2). Even more pleasingly, all of the chiral ABCs shown in Figure 3 produce excellent enantioselectivities in this process (Table 1). HBTM (**6a**)[3d] and its derivatives HBTM-2 (**6b**)[3e] and HBTM-2.1 (**6c**)[8] displayed the highest catalytic activity (entries 6−8). (*R*)-HBTM-2 (**6b**), being currently the most abundant in our lab, was chosen for the subsequent study.

A series of *S*-cinnamoyl derivatives of 2-mercaptobenzaldehyde (**12**) underwent smooth transformation into the

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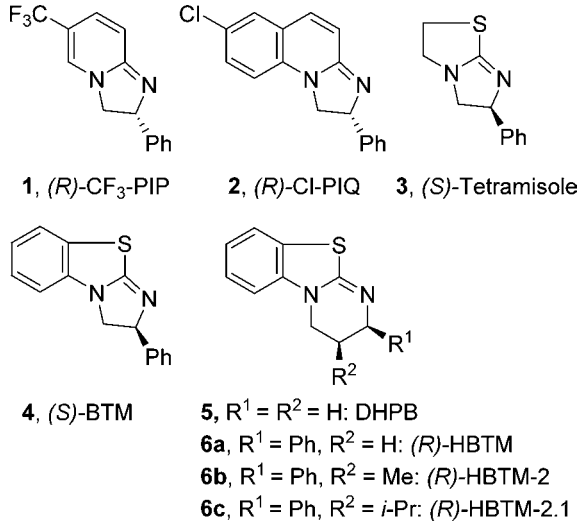
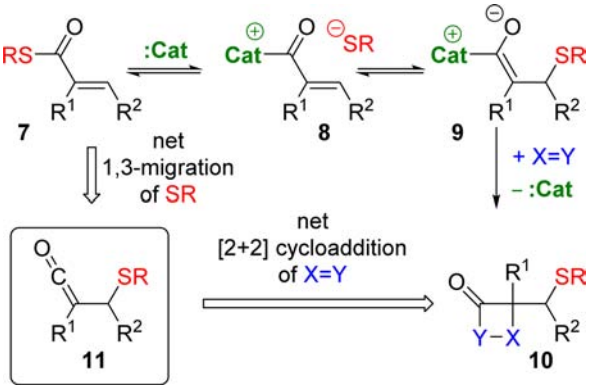
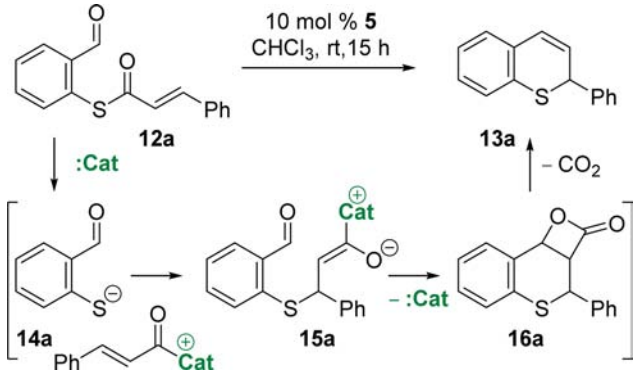


Figure 3. Amidine-based catalysts.

Scheme 1. Proposed Tandem Transformation



Scheme 2. New Synthesis of Thiochromenes



corresponding 2-substituted thiochromenes (**13**) upon treatment with **6b** (Figure 4). Substrates with both electron-donating and electron-withdrawing groups on the aryl substituent R^1 produced excellent yields and outstanding ee values (**13a–g**). An additional aldehyde group in the substrate was tolerated (**13f**). Their heterocyclic analogues also reacted with excellent enantioselectivity, albeit giving somewhat lower yields (**13i**, **13j**). Finally, a substrate with an alicyclic R^1 group produced a comparable result (**13k**). The thiochromene core could also be varied, as shown in Figure 5.

Table 1. Catalyst Survey[a]

entry	catalyst	yield (%)	ee (%)
1	**5**	94	NA
2	(*R*)-**1**	45	99 (*R*)
3	(*R*)-**2**	47	98 (*R*)
4	(*S*)-**3**	25	98 (*S*)
5	(*S*)-**4**	63	99 (*S*)
6	(*S*)-**6a**	98	>99 (*R*)
7	(*R*)-**6b**	99	>99 (*S*)
8	(*R*)-**6c**	99	>99 (*S*)

[a]Conditions: 0.2 M **12a** in $CDCl_3$, 10 mol % catalyst, 23 °C, 15 h.

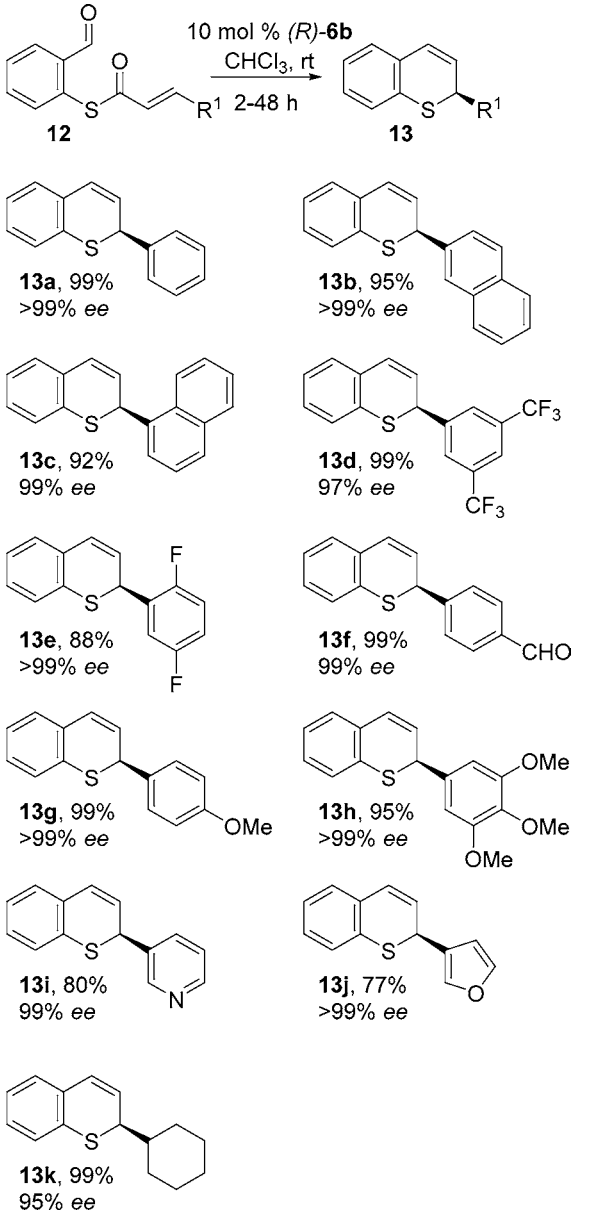


Figure 4. Substrate scope: variation of the side chain.

The absolute configuration of the thiochromene products was predicted on the basis of the transition state model **17a** shown in Figure 6, wherein the conjugate addition of the thiolate occurs from the face opposite the phenyl group on the catalyst. Alternatively, this process may be envisioned as a hetero-Diels–Alder reaction, with the C–S and C–C bonds

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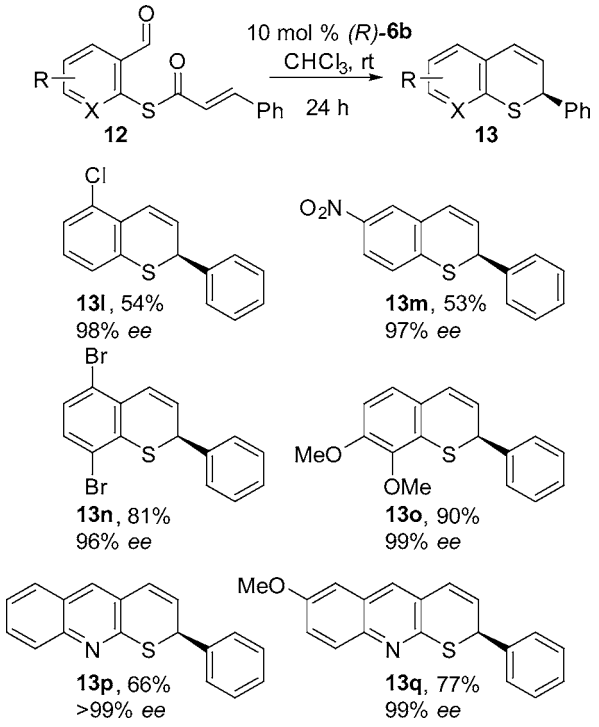

Figure 5. Substrate scope: variation of the thiochromene core.

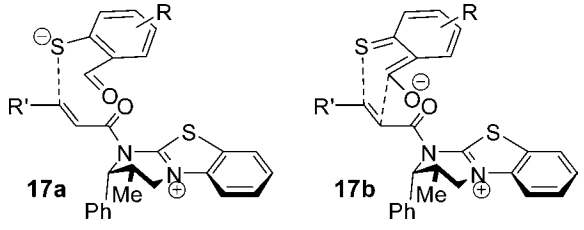

Figure 6. Transition state models.

forming in a concerted fashion (cf. **17b**). The anomalous diffraction X-ray structure[9] of **13q** (Figure 7) provided experimental corroboration of our prediction.

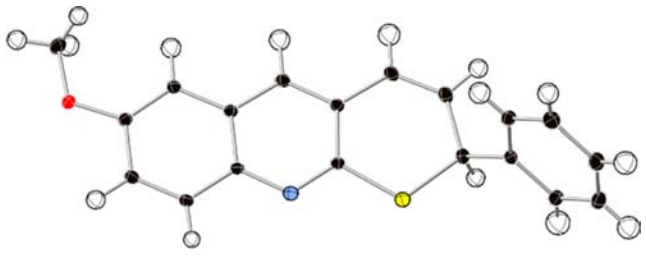

Figure 7. X-ray structure of **13q**. The absolute configuration was determined from the Flack parameters.[9]

In conclusion, we have developed a highly enantioselective synthesis of chiral 2-substituted thiochromenes and their heterocyclic analogues. The new transformation has a broad substrate scope, does not require any added reagents, and generates carbon dioxide as the only byproduct.[10] It also demonstrates for the first time that acyl transfer catalysts can activate thioesters—chromatographically stable, moderately reactive acyl donors. The ramifications of these findings are being investigated in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01639.

General procedures for the synthesis of thioester substrates and thiochromenes, spectral data for new compounds, crystallographic data for **13q**, and HPLC data for thiochromenes (PDF)

X-ray data for **13q** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) Carbon dioxide produced in the reaction was detected and quantified in the form of barium carbonate. See the Supporting Information for details.

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