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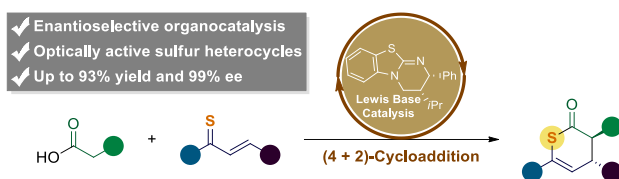
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Isothiourea-Catalyzed Enantioselective Synthesis of *trans*-3,4-Dihydrothiopyranones: Harnessing Thiochalcones as Original Michael Acceptors

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Supporting Information Placeholder



ABSTRACT: Highly enantioselective formal (4 + 2)-cycloaddition between carboxylic acids and thiochalcones promoted by (+)-HBTM-2.1 isothioureia organocatalyst has been reported. The methodology relied on the generation of C1-ammonium enolate intermediates and proceeded through a nucleophilic 1,4-addition-thiolactonization cascade. It enabled the stereocontrolled preparation of sulfur-containing δ -thiolactones in good yields, moderate diastereoselectivity and excellent enantiomeric excess (up to 99%). This annulation benefited from the peculiar reactivity of uncommon electron-rich thiochalcones used as Michael acceptors.

Chiral dihydropyranones constitute a class of heterocycles that have attracted particular interest due to their occurrence in pharmaceuticals as well as in precursors of natural products.¹ Because of their importance, many efforts have been devoted to their efficient catalytic enantioselective synthesis.² Surprisingly, the asymmetric access to dihydrothiopyranones – their sulfur-containing analogues – has been scarcely investigated, despite their promising biological activities.³ To date, only one enantioselective methodology has been proposed by Biju *et al.* in which *N*-heterocyclic carbene promoted (3 + 3)-annulation between 2-bromoaldehydes and β -oxodithioesters providing dihydrothiopyranones in high enantioselectivities (Scheme 1a).⁴ Therefore, the development of a novel stereocontrolled synthetic route for the construction of dihydrothiopyranones is still highly desirable and meet our longtime interest in the asymmetric synthesis of heterocyclic scaffolds.⁵

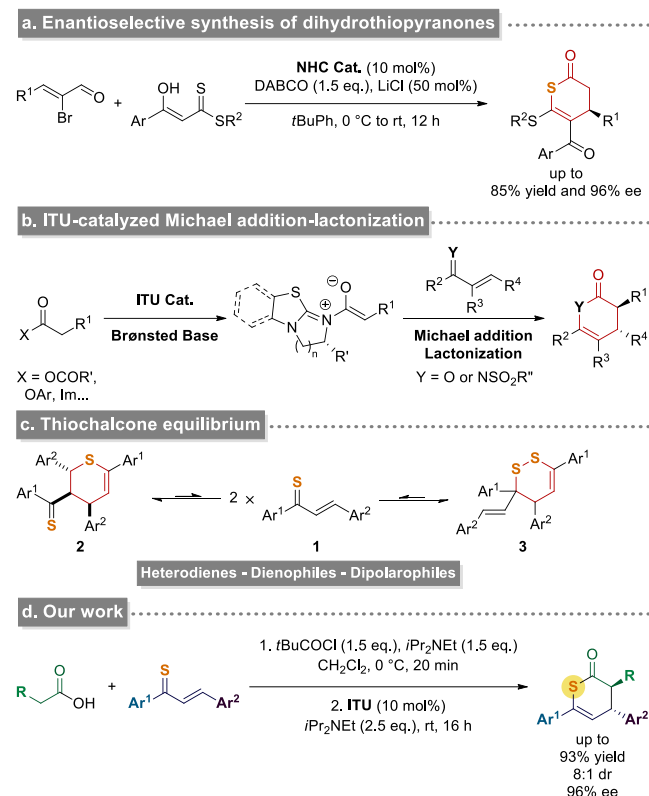
To achieve this goal, we turned our attention to a class of Lewis base, chiral isothioureias (ITUs), popularized by Birman,^{6a} Romo,^{6b} Porco^{6c} and Smith,^{6d} which have recently emerged as privileged organocatalysts for the enantioselective activation of carboxylic acids.⁷ Catalytic event typically starts with the condensation of chiral ITU with carboxylic acid derivative, resulting in the formation of various reactive intermediates such as acylisothiuronium salt or acylisothiuronium enolate (Scheme 1b) that have a wide range of synthetic applications.⁸ In particular, the latter zwitterionic species, displaying a nucleophilic site and a latent electrophilic site, has found broad utility in a variety of enantioselective transformations including formal cycloadditions.^{7,8} Recently, the group of Smith and others have disclosed elegant enantioselective Michael addition-lactonization/lactamization cascades with α,β -unsaturated

enones and imines providing efficient access to dihydropyranones and dihydropyridinones with excellent di- and enantioselectivities (Scheme 1b).⁹ Inspired by these seminal works, we wondered whether thiochalcones could react as suitable partners in a similar cascade reaction in the presence of an ITU catalyst. This would offer a direct and convenient approach for the enantioselective synthesis of targeted dihydrothiopyranones.

However, developing such transformations with this thioated substrates is challenging. First, they are relatively more electron-rich and thus significantly less reactive compared to Michael acceptors commonly used in that kind of methodologies including trihalogenomethylenes^{9c,e} or α -keto- β,γ -unsaturated phosphonates.^{9d} In addition, although the use of thiochalcones as heterodienes in Diels-Alder reactions has been extensively studied by the groups of Motoki, Saito, Mloston and others,¹⁰ their involvement in other cycloadditions – notably as dipolarophiles¹¹ or dienophiles¹² – is relatively new and remains elusive. Eventually, thiochalcones **1** cannot be isolated as monomers because they spontaneously dimerize to generate complex mixtures of thia-Diels-Alder adducts in which 3,4-dihydro-2*H*-thiopyrans **2** and 3,4-dihydro-1,2-dithiines **3** are the major isomers (Scheme 1c).¹² Hence, concentration of active monomeric thiochalcone is low rendering the overall cascade process ambitious when combined with the reversibility of the ammonium enolate formation.^{8b}

Herein we report an isothioureia-catalyzed formal (4 + 2)-cycloaddition of carboxylic acids with thiochalcones, affording a variety of dihydrothiopyranones in good yields with high enantioselectivities and moderate to high diastereoselectivities (Scheme 1d).

Scheme 1. (3 + 3)-Cycloaddition for the Enantioselective Construction of Dihydrothiopyranones, Isothiourea-Catalyzed Michael Addition-Lactonization Cascade and Present Work



Encouragingly, reacting thiochalcone **1a** with an anhydride, generated *in situ* from 2-phenylacetic acid (**4a**) and pivaloyl chloride, in the presence of (+)-HBTM-2.1 (**5a**, 10 mol%), *i*Pr₂NEt and Na₂CO₃ in dichloromethane at room temperature provided desired dihydrothiopyranone **6a** in 21% yield and 89% ee (Table 1, entry 1).¹³ Diastereoselectivity of the reaction was difficult to determine due to ¹H NMR signals overlapping. However, a 5.5:1 dr was roughly estimated in favor of the *trans*-isomer. The cascade remained sluggish even when an excess of carboxylic acid was used (entry 2). In order to increase the concentration of monomeric thiochalcone form, 5 equiv of **1a** was employed and it resulted in dramatically enhanced yield (74%, entry 3). It is noteworthy that 77% of the excess of **1a** could be cleanly recovered through silicagel column chromatography. After screening other solvents such as acetonitrile, THF or toluene (entries 4–6), CH₂Cl₂ proved to be the best one in term of yield and enantioselectivity. Then, we speculated that increasing reaction temperature might favor the overall process by shifting the equilibrium toward the formation of the active monomeric thiochalcone species. However, conducting the reaction at 50 °C in 1,2-dichloroethane (entry 7) markedly decreased the yield of **6a** presumably due to its degradation. Reducing the catalyst loading to 5 mol% could also give a reasonable yield (entry 9). Changing the catalyst to (–)-BTM (**5b**) delivered the desired product in lower yield and enantioselectivity (entry 8). Further optimization revealed that Na₂CO₃ had no visible impact on the transformation (entry 10). Contrary to other ITU-catalyzed reactions, the use of a catalytic amount of HOBT had no positive influence on the stereocontrol.¹⁴

With the best conditions in hand, we next explored the scope of the isothiourea-promoted Michael addition-thiolactonization cascade by using diverse carboxylic acids (Scheme 2). Levels of enantioselectivity were generally satisfactory but diastereoselectivity was variable (4:1–9:1 dr).

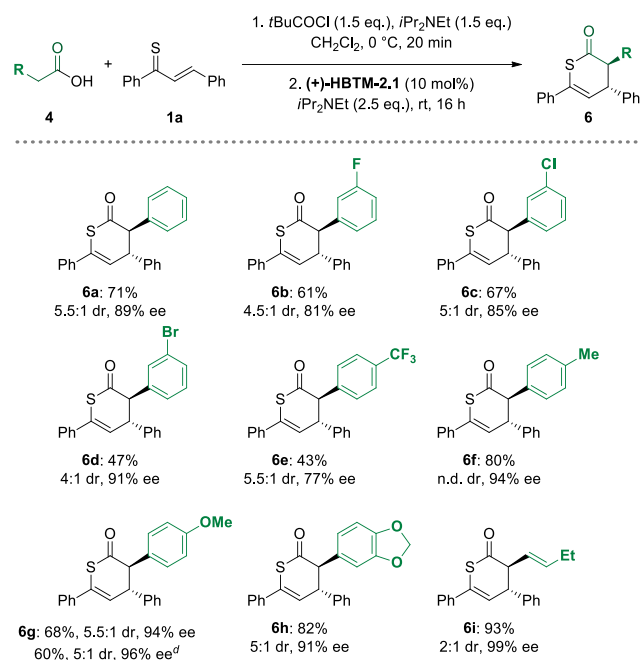
Table 1. Optimization of Reaction Conditions^{a,b}

entry	catalyst (mol%)	ratio 4a/1a (X:Y)	solvent	yield ^c (%)	ee ^d (%)
1	5a (10)	1:1	CH ₂ Cl ₂	21	89
2	5a (10)	2.5:1	CH ₂ Cl ₂	33	89
3	5a (10)	1:5	CH ₂ Cl ₂	74	89
4	5a (10)	1:5	CH ₃ CN	47	81
5	5a (10)	1:5	THF	40	82
6	5a (10)	1:5	toluene	39	87
7 ^e	5a (10)	1:5	(CH ₂ Cl) ₂	25	82
8	5b (10)	1:5	CH ₂ Cl ₂	35	–41
9	5a (5)	1:5	CH ₂ Cl ₂	57	91
10^f	5a (10)	1:5	CH₂Cl₂	71	89
11 ^{f,g}	5a (10)	1:1	CH ₂ Cl ₂	44	83

^aReaction conditions: **4a** (X equiv × 0.1 mmol), **1a** (Y equiv × 0.1 mmol), *i*Pr₂NEt (X equiv × 0.15 mmol), *t*BuCOCl (X equiv × 0.15 mmol), solvent (0.5 mL), 0 °C, 20 min then Na₂CO₃ (X equiv × 0.2 mmol), *i*Pr₂NEt (X equiv × 0.25 mmol), **5** (0.01 mmol), rt, 16 h. ^bDihydrothiopyranone **6a** was obtained as a diastereoisomeric mixture, the dr (ca. 5.5:1) of which could not be precisely determined by ¹H NMR spectroscopic analysis of the crude due to peaks overlap. ^cIsolated yields. ^dDetermined by HPLC analysis on a chiral stationary phase. ^eSecond step at 50 °C. ^fWithout Na₂CO₃. ^gWith HOBT (0.02 mmol).

Electron-depleted substrates were tolerated, delivering the dihydrothiopyranones in decent yields. Pleasingly, phenylacetic acids with *meta*-halogenoaryl groups afforded the desired adducts **6b** and **6c** in respectable yields and enantioselectivities. A slight increase in the enantioselectivity was observed with 3-bromo-substituted thiochalcone (**6d**, 91% ee). 4-(Trifluoromethyl)phenylacetic acid (**4e**) reacted also well leading to **6e** in slightly reduced yield and ee in line with what had been depicted in previous publications.^{9b,c} Carboxylic acids substituted by electron-rich arenes such as 4-methylphenyl and 4-methoxyphenyl were smoothly converted into the corresponding dihydrothiopyranones (**6f** and **6g**) in good yields, enantio- and diastereoselectivities. Acid **4h** bearing more sterically demanding benzo[*d*][1,3]dioxole provided the desired product **6h** in 82% yield with 91% ee and 5:1 dr. Finally, the reaction with a carboxylic acid substituted by an alkene group,^{9c} gave **6i** in excellent yield and enantioselectivity albeit with a moderate dr.

Scheme 2. Carboxylic Acid Scope for the Isothiourea-Catalyzed Michael Addition-Thiolactonization^{a,b,c}



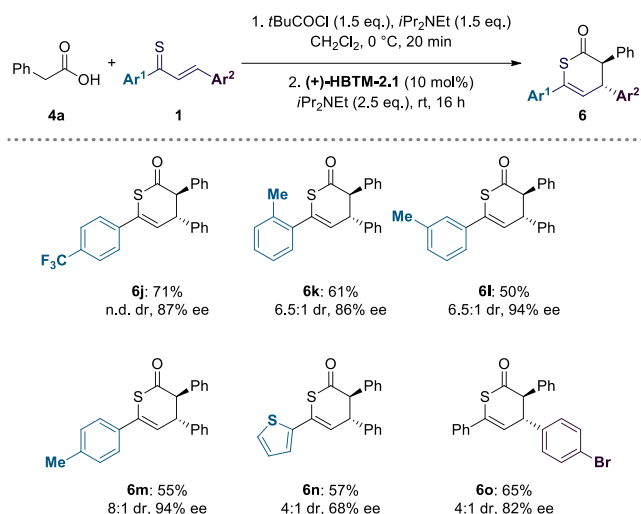
^aReaction conditions: **4** (0.1 mmol), **1a** (0.5 mmol), *i*Pr₂NEt (0.15 mmol), *t*BuCOCl (0.15 mmol), CH₂Cl₂ (0.5 mL), 0 °C, 20 min then *i*Pr₂NEt (0.25 mmol), **5a** (0.01 mmol), rt, 16 h. ^bIsolated yields. ^cThe ee values were determined by HPLC analysis on a chiral stationary phase. The dr values were determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. ^dOn 1.0 mmol scale with 2.5 mmol of **1a**.

The scope of Michael addition-thiolactonization sequence between 2-phenylacetic acid (**1a**) with various thiochalcone derivatives was also surveyed (Scheme 3). The electronic properties of the C1-aryl ring did not greatly affect the stereoselectivity and had a little effect on the yield. For instance, thiochalcone **1b** with *para*-trifluoromethyl moiety on the aromatic substituents led to dihydrothiopyranone **6j** in 71% yield and 87% ee. Electro-enriched thiochalcones, which preferentially adopt the most stable dimeric form (3,4-dihydro-2*H*-thiopyran, **2**), and are consequently less prone to retro-cyclization,¹² underwent cycloaddition to give **6k-m** in satisfactory yields (40–88%) with high enantio- (89–99% ee) and diastereoselectivities (up to 8:1 dr). Similarly, heterocycle-containing 3-phenyl-1-(thiophen-2-yl)prop-2-ene-1-thione (**1f**)^{10d} – a substrate that had been proven challenging in some earlier cycloadditions^{–12} provided product **6n** in 57% yield and 68% enantiomeric excess. Thiochalcone **1g** with 4-bromophenyl ring as the C3-substituent, was also a suitable partner, giving dihydrothiopyranone **6o** in 65% yield and 82% ee. The absolute configuration of **6e** (3*S*,4*R*) was established by X-ray crystal-structure analysis. That of the other compounds reported herein were assigned by analogy.

To demonstrate the robustness of the protocol, a scale-up reaction was performed with a reduced amount of thiochalcone. As shown in Scheme 2, cycloadduct **6g** was obtained in a slightly lower yield with a maintained 96% enantioselectivity. The synthetic utility of dihydrothiopyranones **6** was demonstrated by several modifications (Scheme 4). Base-mediated methanolysis of **6g** provided unstable thioenol intermediate **7**. Subsequent acetylation with acetyl chloride furnished isolable

product **8** in good yield without any erosion of enantioselectivity (Scheme 4a). However, decrease of the diastereoselectivity was noted. In addition, subjecting allylic product **6i** to an excess of base led to the thermodynamically-favored isomer **9** (Scheme 4b) in moderate yield but retained enantiomeric excess.

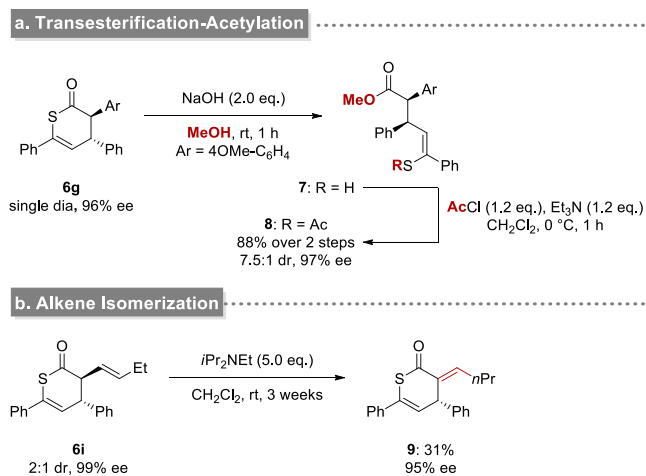
Scheme 3. Thiochalcone Scope for the Isothiourea-Catalyzed Michael Addition-Thiolactonization^{a,b,c}



^aReaction conditions: **4a** (0.1 mmol), **1** (0.5 mmol), *i*Pr₂NEt (0.15 mmol), *t*BuCOCl (0.15 mmol), CH₂Cl₂ (0.5 mL), 0 °C, 20 min then *i*Pr₂NEt (0.25 mmol), **5a** (0.01 mmol), rt, 16 h. ^bIsolated yields. ^cThe ee values were determined by HPLC analysis on a chiral stationary phase. The dr values were determined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

To gain further information about the mechanism of the reaction, some control experiments were carried out. First, the evolution of the equilibrium between 3,4-dihydro-2*H*-thiopyran **2** and 3,4-dihydro-1,2-dithiin **3** thiochalcone major isomers was monitored for a period of 4 hours via ¹H NMR analysis. The fraction of most stable dimer **2** slightly increased over the time at the expense of adduct **3**. Moreover, **2**/**3** ratio was not affected by the addition of 1 equiv of *i*Pr₂NEt or 10 mol% of catalyst **5a** suggesting they had no influence on this equilibration (see the Supporting Information).

Scheme 4. Synthetic Transformations of products 6



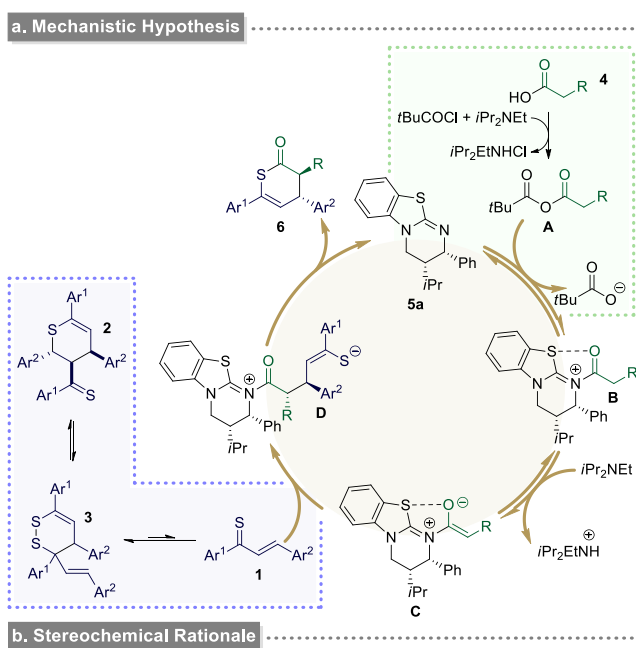
Noteworthy, no cycloaddition occurred when *trans*-1,3-diphenylprop-2-en-1-one (chalcone, **10**) was used as the Michael

acceptor under optimized conditions, highlighting the peculiar properties of our sulfur-containing conjugated substrates (see the Supporting Information). Ultimately, the diastereomeric stability of dihydrothiopyranones was examined by treating **6g** with an excess of *i*Pr₂NEt. Its dr remained unchanged, which indicates that no epimerization occurs during the cascade reaction (for further details see the Supporting Information).

Based on earlier studies disclosed by Smith *et al.* and results obtained above, a plausible mechanism is proposed in Scheme 5.^{9c} Addition of nucleophilic ITU catalyst to mixed anhydride **A** generated *in situ*, leads to acylisothiuronium cation **B**. Its subsequent deprotonation/enolization affords the chiral zwitterionic (*Z*)-acylisothiuronium enolate **C**.⁸ The latter undergoes a stereoselective Michael addition on monomeric thiochalcone **1** released, at low concentration, in the reaction mixture from its 3,4-dihydro-2*H*-thiopyran **2** and 3,4-dihydro-1,2-dithiin **3** dimeric forms by a retro-Diels-Alder reaction. Afterward, the obtained Michael adducts **D** cyclizes to furnish desired thiolactone derivative **6** with concomitant regeneration of catalyst **5a**.

The asymmetric induction can be explained using the classical rationale developed for chiral ITUs and supported by DFT calculations. Stabilizing non-covalent O–S interaction (*n*_O to σ_{C-S}* overlap) locks the conformation of acylisothiuronium enolate **C** orienting the phenyl group of the ITU in a pseudoaxial position which shields its *Si*-face.¹⁵ The stereoselectivity of the reaction can be then predicted using a Heathcock's model¹⁶ with staggered conformation minimizing non-bonding interactions.¹⁷

Scheme 5. Postulated Mechanism and Stereochemical Rationale



To conclude, a mild enantioselective synthesis of *trans*-dihydrothiopyranones promoted by isothioureia organocatalyst has

been developed. It provided optically active δ-thiolactones in decent to good yields, moderate diastereoselectivity and high enantiomeric excess using carboxylic acid and thiochalcone building blocks. The latter Michael acceptors are singularly electron-rich which is unprecedented in such C1-ammonium enolate 1,4-addition-lactonization cascade, underlining the unique properties of thiocarbonyl derivatives. The cycloaddition could be easily scaled-up and the obtained adducts was opened thanks to a transesterification reaction.

ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data. (PDF)

Accession Codes

CCDC 2268278 contain the supplementary crystallographic data for this paper. They can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 (0)1223 336033.

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Notes

The authors declare no competing financial interest.

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