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Asymmetric Synthesis of Chiral Dihydrothiopyrans via an Organocatalytic Enantioselective Formal Thio [3 + 3] Cycloaddition Reaction with Binucleophilic Bisketone Thioethers

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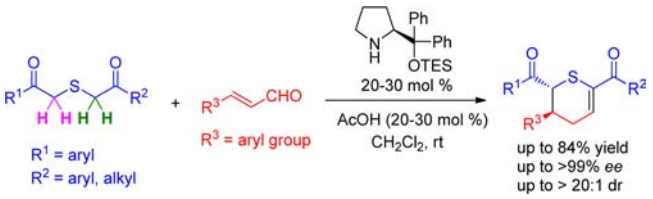
ABSTRACT



An unprecedented organocatalytic highly enantioselective approach to a 3,4-dihydro-2*H*-thiopyran scaffold with two contiguous stereogenic centers has been implemented through a formal thio [3 + 3] cycloaddition process involving a Michael−aldol condensation cascade sequence. Notably, a new class of binucleophilic bisketone thioethers is designed for the process. Furthermore, the fine-tuning of their reactivity enables the cascade process to proceed with highly regioselectively.

3,4-Dihydro-2*H*-thiopyrans are widely distributed in a number of biologically active compounds (Figure 1). They exhibit interesting pharmacological properties, such as antipsoriatic (**1a**),[1] antiviral (**1b**),[2] and antiatherosclerosis (**1c**).[3] Significant work has been performed on the synthesis of the frameworks in racemic form.[4] The most widely used strategy employs the thio-Diels−Alder reaction with thioaldehydes, thioketones, or their α,β-unsaturated equivalent, 1-thiabuta-1,3-dienes.[4a−c,5,6] In addition, the asymmetric version of the thio-Diels−Alder reactions has

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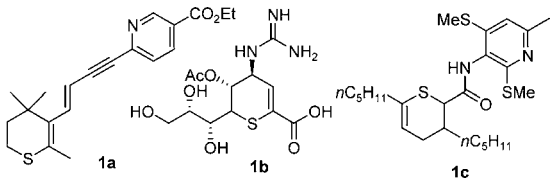

Figure 1. Representative bioactive molecules containing a 3,4-dihydro-2*H*-thiopyran unit.

also been explored using chiral auxiliaries.[7] Very recently, Jørgensen et al. reported the first organocatalytic enantioselective thio-Diels–Alder reactions, leading to chiral 3,6-dihydro-2*H*-thiopyrans.[8]

While significant efforts have been made on the synthesis of the dihydrothiopyrans using the most popular [4 + 2] cycloaddition methods, formal [3 + 3] cycloaddition reactions offer an alternative approach to creating structurally different architectures of the 6-membered rings.[9,10] In this context, notably Hsung and co-workers developed a series of highly useful methods for the synthesis of 6-membered ring structures.[10] Although catalytic enantioselective methods are appealing, the examples are extremely rare.[9b–f] Hong, Tang, and Hayashi independently reported efficient organocatalytic enantioselective [3 + 3] ring formation of enantioenriched cyclohexanes,[9b–d] and Hayashi and our group disclosed approaches to chiral piperidines.[9e,f] Nevertheless, to the best of our knowledge, organocatalyzed [3 + 3] cycloaddition has not been reported for the formation of chiral dihydrothiopyrans. Toward this end, we wish to report the first asymmetric construction of 3,4-dihydro-2*H*-thiopyran framework with creation of two contiguous stereogenic centers catalyzed by diphenylprolinol silyl ethers[11] under mild reaction conditions using newly designed binucleophilic bisketone thioethers **2** reacting with enals **3** (Scheme 1).[12–14]

In the design of a proposed organocatalyzed formal [3 + 3] cyclcoaddition reaction to generate requisite 3,4-dihydro-2*H*-thiopyrans, a new class of binucleophilic bisketone thioethers **2** is designed. It is conceived that the bisketone moiety in **2** renders the two "CH_2" acidic to produce two contingent nucleophilic species for the initial Michael addition and subsequent aldol-condensation reaction (Scheme 1). Therefore, they should be nucleophilically active enough to participate in the Michael and aldol–condensation cascade process. In addition, the differentiation of the reactivities of the two similar nucleophilic "CH_2" moieties presents an important challenge when R^1 and R^2 are not the same since this directly affects the nature of products formed. It is desired that the more active "CH_2" reacts first in the initial Michael reaction while the less active one engages in the subsequent intramolecular aldol-condensation process.

To probe the validity of the proposed organocatalytic thio [3 + 3] cycloaddition process, we probed a model reaction by using simple symmetric 2,2′-thiobis(1-phenylethanone) **2a** with *trans*-cinnamaldehyde **3a** catalyzed by diphenylprolinol silyl ether (**I**) in the initial attempt (Table 1). To our delight, the reaction proceeded smoothly to afford the desired 3,4-dihydro-2*H*-thiopyran **4a** in good yield (69%, entry 1), with excellent enantioselectivity (ee >99%) and moderate diastereoselectivity (70:30 dr). This encouraging result proved our working hypothesis. Moreover, we demonstrated that the newly designed

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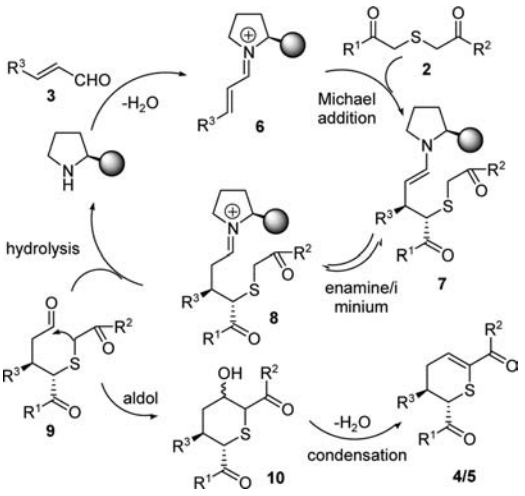
Scheme 1. Proposed Mechanism for the Designed Formal [3 + 3] Cycloaddition Involving a Michael–Aldol Condensation Cascade Sequence

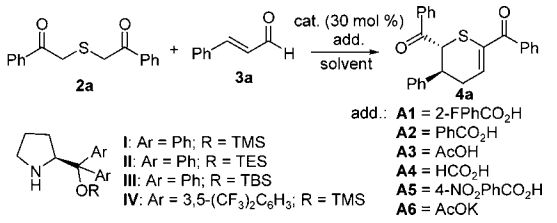


binucleophilic bisketone thioethers could serve as nucleophiles in mild organocatalytic reactions. Often used chiral diarylpyrrolidine silyl ether catalysts **II**–**IV** were screened next.

Improved diastereoselectivity (75:25 dr) and excellent enantioselectivity (ee >99%) were also obtained with catalyst **II** (entry 2), although a longer reaction time (3.5 d) was required. In contrast, incomplete conversion and relatively lower ee values were observed for catalysts **III** and **IV**, which bear more bulky side-chain moieties (entries 3 and 4). It was found that acid additives were beneficial to the diastereoselectivity (entries 5–13). With catalyst **II** in the presence of 2-fluorobenzoic acid as the additive, 92:8 dr was achieved (entry 5). Moreover, the reaction time was also reduced to 16 h. Further optimization of reaction conditions including screening of solvents and additives (entries 5–16) led us to select the protocol consisting of catalyst **II** in the presence of AcOH in CH_2Cl_2 to probe the scope of the formal [3 + 3] cycloaddition reaction (entry 11).

Substrate **2a** reacting with structurally diverse enals **3** under the optimized conditions was examined (Table 2, entries 1–10). It is shown that the protocol serves as the general procedure for the synthesis of enantioentriched 3,4-dihydro-2*H*-thiopyrans **4**. The desired products were obtained with good to excellent ee values (84–99%). It appears that the substitution pattern and electronic nature of the substituents on the benzene ring of enals have an unpredicted manner on the diastereoselectivity. For instance, 4-*N*,*N*-dimethyl and 2-NO_2 moieties resulted in excellent diastereoselectivity (95:5 and >20:1 dr, respectively, entries 6 and 7), whereas 4-MeO, 4-Br, 4-NO_2, and 2-MeO offered moderate dr values (entries 2–5). In addition to phenyl-substituted enals, fused aromatic and heterocyclic systems such as furanyl and thienyl (entries 8–10) were also well tolerated and afforded the products in good yield (74–84%) and with excellent ee values (97–99%). However, no reaction was observed for the aliphatic enals (data not shown).

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	add.	solvent	time	yield[b] (%)	dr[c]	% ee[d]
1	**I**		CH_2Cl_2	2 d	69	70:30	>99
2	**II**		CH_2Cl_2	3.5 d	68	75:25	>99
3	**III**		CH_2Cl_2	7 d	52	71:29	92
4	**IV**		CH_2Cl_2	7 d	32	ND[e]	ND
5	**II**	**A1**	CH_2Cl_2	16 h	72	92:8	95
6	**II**	**A1**	PhMe	30 h	50	64:36	>99
7	**II**	**A1**	EtOEt	30 h	36	93:7	>99
8	**II**	**A1**	$CHCl_3$	30 h	43	84:16	>99
9	**II**	**A1**	CH_3CN	30 h	41	70:30	>99
10	**II**	**A2**	CH_2Cl_2	12 h	73	85:15	97
11	**II**	**A3**	CH_2Cl_2	36 h	72	90:10	>99
12	**II**	**A4**	CH_2Cl_2	24 h	<10	ND	ND
13	**II**	**A5**	CH_2Cl_2	36 h	50	76:24	>99
14	**II**	**A6**	CH_2Cl_2	7 d	64	66:34	98
15[f]	**II**	**A3**	CH_2Cl_2	5 d	71	81:19	>99
16[g]	**II**	**A3**	CH_2Cl_2	5 d	76	81:19	99

[a] Reaction conditions (unless otherwise specified): solvent (1.5 mL), 2,2′-thiobis(1-phenylethanone) **2a** (0.11 mmol, 1.0 equiv), cinnamaldehyde **3a** (0.13 mmol, 1.2 equiv), catalyst (30 mol %), additive (30 mol %), rt. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] Not determined. [f] Catalyst (20 mol %), additive (20 mol %). [g] Catalyst (20 mol %), additive (50 mol %).

A similar trend was observed with various symmetric thio-diketones **2** (entries 11–16). Nevertheless, when the aromatic ring bore a 2-nitro group in the enal, under the standard conditions, the desired product **4q** was obtained with excellent stereoselectivities (>20:1 dr and 97% ee), but the yield was decreased (46%). Further optimization of reaction conditions with addition of 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea as additive, a similar protocol reported by Xu et al.,[15] led to significant improvement of the reaction yield (72%), shortened reaction time (36 h), and reduced catalyst loading (20 mol %) while achieving comparable enantio- and diastereoselectivity (entries 17–19). The absolute configuration of the adducts was determined based on the derivative **11** derived from compound **4g** with (2*R*, 3*S*) configuration (Figure S1, Supporting Information).[16]

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(16) The structure of compound **11** derived from molecule **4g** was determined by X-ray crystal analysis. CCDC-958271 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk and see the Supporting Information.

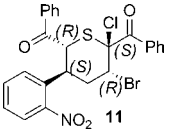
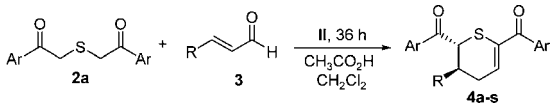


Table 2. Substrate Scope of the Asymmetric formal [3 + 3] Cycloaddition[a]



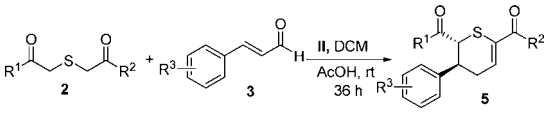
entry	pro.	Ar, R	yield[b] (%)	dr[c]	% ee[d]
1	**4a**	Ph, Ph	72	90:10	>99
2	**4b**	Ph, 4-$CH_3OC_6H_4$	79	78:22	84
3	**4c**	Ph, 4-BrC_6H_4	72	73:27	96
4	**4d**	Ph, 4-$NO_2C_6H_4$	66	74:26	93
5	**4e**	Ph, 2-$CH_3OC_6H_4$	85	80:20	99
6	**4f**	Ph, 4-$(CH_3)_2NC_6H_4$	66	95:5	95
7	**4g**	Ph, 2-$NO_2C_6H_4$	63	>20:1	99
8	**4h**	Ph, 2-naphthyl	74	76:24	99
9	**4i**	Ph, 2-furanyl	84	76:24	97
10	**4j**	Ph, 2-thienyl	75	73:27	97
11	**4k**	4-ClC_6H_4, Ph	68	90:10	94
12	**4l**	4-BrC_6H_4, Ph	65	73:27	95
13	**4m**	2-FC_6H_4, Ph	61	75:25	>99
14	**4n**	2-ClC_6H_4, Ph	75	68:32	95
15	**4o**	3-FC_6H_4, Ph	72	72:28	89
16	**4p**	2-thienyl, Ph	80	90:10	91
17[e]	**4q**	4-$CF_3C_6H_4$, 2-$NO_2C_6H_4$	72	>20:1	97
18[e]	**4r**	2-FC_6H_4, 2-$NO_2C_6H_4$	74	>20:1	95
19[e]	**4s**	3-FC_6H_4, 2-$NO_2C_6H_4$	70	>20:1	86

[a] Unless specified, reactions were performed with **2a** (0.11 mmol), **3** (0.13 mmol, 1.2 equiv), catalyst **II** (30 mol %), and AcOH (30 mol %) in CH_2Cl_2 (1.5 mL) at rt for 36 h. [b] Isolated yields. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Catalyst **II** (20 mol %), 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea (20 mol %) and AcOH (20 mol %) were added to the solution.

Finally, we turned our attention to the highly challenging unsymmetrical thiodiketones **2** for the Michael–aldol condensation cascade reaction with enals. Guided by the principle of the electronic effect on reactivity, we first designed and probed an unsymmetrical bisarylketone thioether, where one aromatic ring possesses a strong EWG *p*-NO_2. We found that two regioisomers with ca. 3:1 ratio were formed. Then we designed the diketones bearing respective aryl and alkyl groups, which makes their nucleophilicity different enough, where aryl ketone is more active (Table 3). In the initial attempt, we used phenyl and highly steric *tert*-butyl diketone (entry 1). To our delight, the process occurred exclusively regioselectively under the standard reaction conditions. Furthermore, impressively high enantio- (93% ee) and diastereoselectivity (>20:1) were achieved in 60% yield. We also extended the strategy to less hindered aliphatic ketones: isopropyl (entry 2), isobutyl (entry 3), and methyl (entry 4). Moreover, there is a limited impact on the reaction efficiency with the variation of the aromatic structures in both enals and aryl ketones (entries 5 and 6).

The obtained highly functionalized enantioenriched dihydrothiopyrans can be readily converted into complex molecular structures. For example, compound **4g** can be transformed into a new scaffold **12** (Scheme 2) bearing four stereogenic centers with good yield (66%) and great stereocontrol (92% ee, 91:9 dr) via a one-step Nazarov reaction.

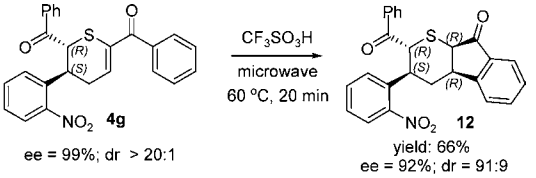
Table 3. Substrate Scope of Thiodiketone **2** Involved in the [3 + 3] Cycloaddition[a]



entry	pro.	R^1, R^2, R^3	yield[b] (%)	dr[c]	ee[d] (%)
1	**5a**	Ph, *tert*-butyl, H	60	>20:1	93
2	**5b**	Ph, isopropyl, H	64	>20:1	97
3	**5c**	Ph, isobutyl, H	66	>20:1	93
4	**5d**	Ph, methyl, H	51	85:15	97
5	**5e**	4-BrC_6H_4, *tert*-butyl, H	73	>20:1	90
6	**5f**	4-BrC_6H_4, *tert*-butyl, 4-Br	66	>20:1	99

[a] Reactions were performed with **2** (0.11 mmol), **3** (0.13 mmol, 1.2 equiv), catalyst **II** (30 mol %), and AcOH (30 mol %) in CH_2Cl_2 (1.5 mL) at rt for specified time. [b] Yield of isolated product after column chromatography. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis.

Scheme 2. Transformation of Michael–Aldol Condensation Adduct **4g** to **12** via a Nazarov Reaction



In summary, we have developed an unprecedented organocatalytic formal [3 + 3] cycloaddition process to create a valuable 3,4-dihydro-2*H*-thiopyran scaffold in good to high yields (up to 84%) and with good diastereo- (up to >20:1 dr) and enantioselectivities (up to >99% ee). Critically, the cascade process relies on newly developed simple binucleophilic bisketone thioethers. Moreover, the careful manipulation of the reactivity of binucleophilic bisketone thioethers enables the cascade process to proceed highly regioselectively to afford the structurally diverse dihydrothiopyrans. Further exploration of the new reagents in the synthesis and the synthetic elaboration of the dihydrothiopyran scaffold and the biological properties of these compounds are currently underway in our laboratories.

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Supporting Information Available. Experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.