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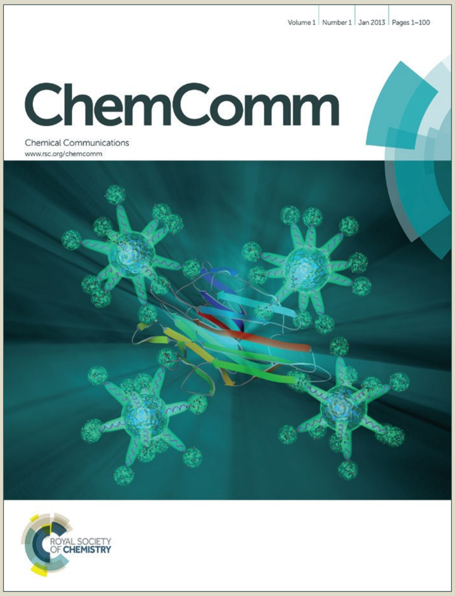

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ARTICLE TYPE

Amine-catalyzed Tunable Reactions of Allenoates with Dithioesters: Formal [4+2] and [2+2] Cycloadditions for the Synthesis of 2,3-dihydro-1,4-oxathiines and Enantioenriched Thietanes

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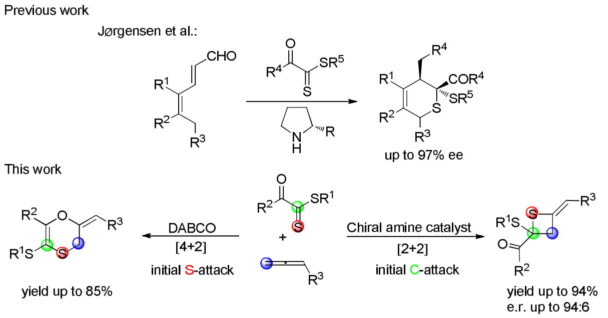
The chemoselective [4+2] vs [2+2] cycloaddition between allenoates and dithioesters can be controlled by switching nucleophilic amine catalyst. The two modes of cyclizations represent the first example of controllable and chemoselective annulations between allenoates and dienophiles catalyzed by amine. These cyclizations are useful in offering a divergent synthesis of sulfur-containing heterocycles. On the basis of this investigation, it can be realized that dithioesters with a vicinal electron-withdrawing group can react not only like a Michael acceptor but also as a ketone or imine.

Lewis base catalysis, often classified as nucleophilic catalysis, remains an active and dynamic area of interest for synthetic chemists. Allenoates as a class of attractive substrates are often used in Lewis base catalyzed reactions due to their facile preparation and diverse reactivity.[1] The addition of a Lewis base to the electrophilic, *sp*-hybridized, β-carbon of an α-allenic ester results in the generation of a zwitterionic enolate-like intermediate which subsequently takes part in divergent annulation reaction modes with alkene, ketone and imine, including [3+2],[2] [4+2],[3] [3+3][4] and [2+2][5] annulations. However, to the best of our knowledge, thiocarbonyls have not been employed in the cycloaddition with allenoates catalyzed by phosphines or amines. In 2013, Jørgensen reported an asymmetric organocatalytic Thio-Diels-Alder reaction between dienals and dithioesters via trienamine catalysis.[6] Based on theoretical investigations, they suggested that this Thio-Diels-Alder Reaction was a stepwise process rather than a concerted [4+2] cycloaddition and dithioesters with a vicinal electron-withdrawing group acted like a Michael acceptor in their reaction (Scheme 1). With these precedents in mind and in connection with our ongoing efforts on developing novel reactions using nitrogen-containing Lewis bases as nucleophilic catalysts,[7] we envisaged that treating allenoates with dithioesters under the catalysis of the nucleophilic amine might afford 2,3-dihydro-1,4-oxathiine derivatives (Scheme 1).



Scheme 1. Amine Catalyzed Cycloaddition Based on Thiocarbonyls

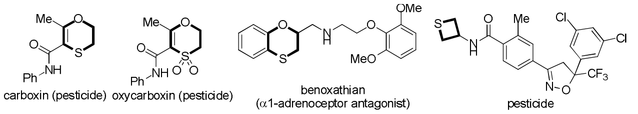


Figure 1. Biologically Active Molecules Containing 1,4-oxathiine or thietane

Gratifyingly, we obtained the expected 1,4-oxathiine derivatives which were generated by a formal [4+2] cycloaddition between allenoates and dithioesters under the catalysis of DABCO. 1,4-oxathiine represents an important structural motif featured in biologically active compounds (Figure 1).[8] For example, Carboxin (Vitavaxa®) and its 4,4-dioxide analogue, oxycarboxin (Plantavaxa®), are well known as systemic fungicides and both are the active components of many effective commercially available pesticides used worldwide to control crop smuts and rust diseases.[9] Motivated by these significances, intensive investigations have been conducted to develop practically useful and step-economic methodologies to the 1,4-oxathiine architecture.[10] Accordingly, the discovery of novel strategies for the synthesis of 1,4-oxathiine with good functional-group tolerance through simple operation is highly desirable. Besides the expected [4+2] cycloaddition products in our experiment, we could also obtain enantioenriched [2+2] cycloaddition products by choosing different chiral catalysts. It remains a challenge to selectively generate different products from identical substrates, utilizing catalyst rather than substrate control. Thietanes also commonly present in a variety of natural products as well as biologically active compounds.[11,12] Although thietanes can be synthesized via a lot of known methods, one-step asymmetric catalysis methodology to construct this scaffold has not been reported.[13] Herein, we wish to report the amine-

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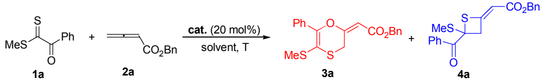
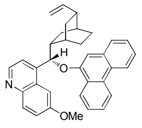
catalyzed tunable cycloadditions between allenoates and dithioesters.

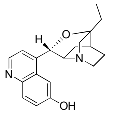
Table 1. Optimization of Reaction Conditions

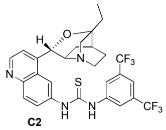


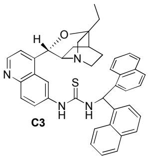
entry[a]	cat.	solvent	T (°C)	yield of **3a** (%)[b]	yield of **4a** (%)[b]	**3a**:**4a**[c]	e.r. of **4a** (%)[d]
1	DABCO	CH_2Cl_2	rt	20	10	2.0:1	-
2	DABCO	toluene	rt	37	7	5.3:1	-
3	DABCO	THF	rt	36	4	9.0:1	-
4	DABCO	DMF	rt	32	trace	-	-
5	DABCO	CH_3CN	rt	33	trace	-	-
6	DABCO	toluene	0	60	12	5.0:1	-
7	DABCO	toluene	-20	75	9	8.3:1	-
8	DABCO	toluene	-40	82	9	9.1:1	-
9	DABCO	toluene	-40	85	9	9.4:1	-
10	quinine	toluene	rt	-	-	-	-
11	$(DHQD)_2PHAL$	toluene	rt	-	-	-	-
12	**C1**	toluene	rt	-	-	-	-
13	β-ICD	THF	rt	30	30	1:1.0	54:46
14	**C2**	THF	rt	30	30	1:1.0	53:47
15	**C3**	THF	rt	47	53	1:1.1	68:32
16	**C3**	toluene	rt	27	71	1:2.6	83:17
17	**C3**	CH_2Cl_2	rt	28	68	1:2.4	64:36
18	**C3**	toluene	0	33	65	1:2.0	83:17
19[e]	**C3**	CH_2Cl_2	rt	27	70	1:2.6	68:32

[a]Dithioester **1a** (0.1 mmol), allenoate **2a** (0.1 mmol), and catalyst (0.02 mmol) were stirred in 1 mL of solvent. [b]Isolated yields after chromatography are shown. [c]Determined by ^1H NMR spectroscopy. [d]Determined by HPLC analysis. [e]10 mol% of catalyst loading.


C1


β-ICD

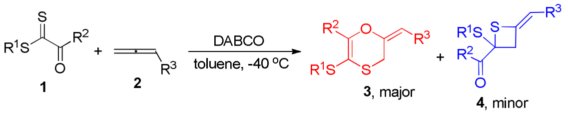

C2


C3

Initial studies using dithioester **1a** and allenoate **2a** as the substrate were aimed at determining the reaction outcome and subsequently optimizing the reaction conditions. The results are summarized in Table 1. We found that [4+2] cycloaddition product **3a** was obtained in 20% yield as a major product with concomitant formation of [2+2] cycloaddition compound **4a** in 10% yield when the reaction was carried out in CH_2Cl_2 under the catalysis of DABCO (20 mol %) at room temperature for 24 h (Table 1, entry 1). Instead of DABCO, other commonly used nitrogen-containing catalysts such as DMAP, DBU and Et_3N were also tested; however, they afforded a complex product mixture under the same reaction conditions. The examination of solvent effects using DABCO (20 mol %) as the catalyst revealed that toluene was the solvent of choice (Table 1, entries 1-5). After extensive screening of reaction temperature, we found that this [4+2] cycloaddition was sensitive to reaction temperature and the reaction provided compound **3a** in 85% yield along with **4a** in 9% yield at -40 °C. Further attempts to switch the regioselectivity to produce **4a** were carried out with **1a** and **2a** using various cinchona alkaloid-derived catalysts. Using Quinine, $(DHQD)_2PHAL$ or **C1** as catalyst, almost all of starting materials **1a** were recovered (Table 1, entries 10-12). When β-ICD was employed as catalyst, this reaction could afford **4a** in 30% yield with 54:46 e. r. value (Table 1, entry 13). We rationalized that the cyclic ether motif of β-ICD is critical to promote the reaction between allenoates and dithioesters because of the reduced steric hindrance around the nucleophilic nitrogen of β-ICD by restraining the conformational freedom of the bulky aromatic moiety.[13] To improve the stereoselectivity, further studies were focused on the effect of hydrogen bonding donor motif of the catalyst on this annulations reaction. Under the catalysis of **C2** which was designed and prepared by Deng, cycloadduct **4a** was obtained in similar results as that of β-ICD (Table 1, entry 14).[14] The reaction could give better results in terms of yield and chemoselectivity in the presence of **C3** containing a sterically hindered thiourea group (Table 1, entry 15). The examination of solvent effects using **C3** (20 mol %) as the catalyst also revealed that toluene was the solvent of choice, affording **4a** in 71% yield with 83:17 e. r. value (Table 1, entries 16-17). Lowering the temperature to 0 °C did not improve the enantioselectivity of this [2+2] cycloaddition (Table 1, entry 18). Reducing the catalyst loading to 10 mol% had no significant influence on the reaction outcome (Table 1, entry 19).

With the optimized reaction conditions in hand, we next investigated the generality of this [4+2] cyclization reaction (Table 2). As for dithioester **1**, both electron-deficient (**1b-1c** and **1e**) and electron-rich (**1d** and **1f**) aromatic substituents at the α-position were tolerated in this [4+2] cyclization reaction although **1d** and **1f** afforded the desired products with lower chemoselectivity (Table 2, entries 1-5). Even for dithioester **1g** having a naphthalen-2-yl group, the corresponding product **3g** was furnished in 81% yield (Table 2, entry 6). We were pleased to find that heteroaromatic group-substituted dithioester **1h** was also suitable for this reaction, affording **3h** in moderate yield (Table 2, entry 7). The structure of compound **3h** was confirmed by X-ray diffraction.[16] Furthermore, the optimized reaction conditions were also applicable to dithioester **1i** bearing an alkyl group at the α-position (Table 2, entry 8). Using dithioester **1j** containing a benzylthio group in this [4+2] cyclization reaction afforded **3j** in 72% yield under the standard conditions (Table 2, entry 9). Notably, besides allenoate **2a**, 1-phenylbuta-2,3-dien-1-one **2b** was also applicable to this [4+2] cyclization reaction without the formation of [2+2] cycloadduct (Table 2, entries 10-15). We reasoned that the better chemoselectivity may be caused by the stronger electron withdrawing ability of the carbonyl group in **2b**.

Table 2. Substrate Scope for DABCO-catalyzed [4+2] Cycloadditions between Allenoates and Dithioesters.



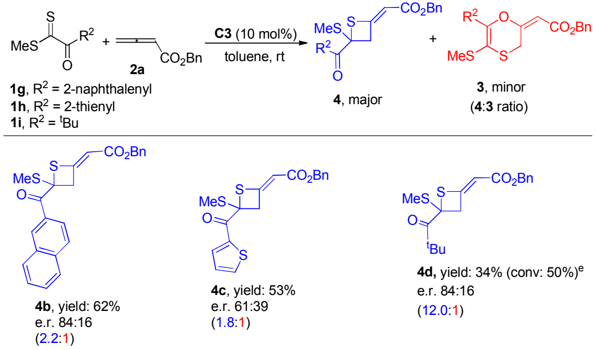
entry[a]	R^1, R^2	R^3	yield of **3** (%)[b]	**3**:**4**[c]
1	**1b**, Me, 2-chlorophenyl	**2a**, CO_2Bn	**3b**, 73	>99:1
2	**1c**, Me, 3-bromophenyl	**2a**, CO_2Bn	**3c**, 71	17.0:1
3	**1d**, Me, 3-methoxyphenyl	**2a**, CO_2Bn	**3d**, 81	11.0:1
4	**1e**, Me, 4-bromophenyl	**2a**, CO_2Bn	**3e**, 76	>99:1
5	**1f**, Me, *p*-tolyl	**2a**, CO_2Bn	**3f**, 78	6.0:1
6	**1g**, Me, 2-naphthalenyl	**2a**, CO_2Bn	**3g**, 81	10.0:1
7	**1h**, Me, 2-thienyl	**2a**, CO_2Bn	**3h**, 52	4.4:1
8	**1i**, Me, ^{t}Bu	**2a**, CO_2Bn	**3i**, 44	1.3:1
9	**1j**, Bn, Ph	**2a**, CO_2Bn	**3j**, 72	16.0:1
10	**1j**, Bn, Ph	**2b**, COPh	**3k**, 68	-
11	**1b**, Me, 2-chlorophenyl	**2b**, COPh	**3l**, 67	-
12	**1c**, Me, 3-bromophenyl	**2b**, COPh	**3m**, 68	-
13	**1e**, Me, 4-bromophenyl	**2b**, COPh	**3n**, 57	-
14	**1g**, Me, 2-naphthalenyl	**2b**, COPh	**3o**, 45	-
15	**1h**, Me, 2-thienyl	**2b**, COPh	**3p**, 43	-

[a]Dithioester **1** (0.2 mmol), allene **2** (0.2 mmol), and DABCO (0.04 mmol) were stirred in 2 mL of toluene at -40 °C. [b]Isolated yields after chromatography are shown. [c]Determined by ^1H NMR spectroscopy.

Using catalyst **C3**, we were able to suppress the [4+2] cycloaddition of allenoates with dithioesters and selectively access thietane products. Under the optimized reaction conditions, we next investigated the generality of this [2+2] cyclization reaction and the results are summarized in Table 3. In the case of dithioester **1g**, the corresponding product **4b** was obtained in 62% yield with 84:16 e. r. value (Table 3). As for **1h**, the reaction afforded thietane **4c** in 53% yield along with 61:39 e. r. value (Table 3). However, using dithioester **1i** as substrate, the reaction became sluggish so that the conversion of dithioester **1i** was only 50% after 2 days, affording thietane **4d** in 34% yield with 84:16 e. r. value (Table 3).

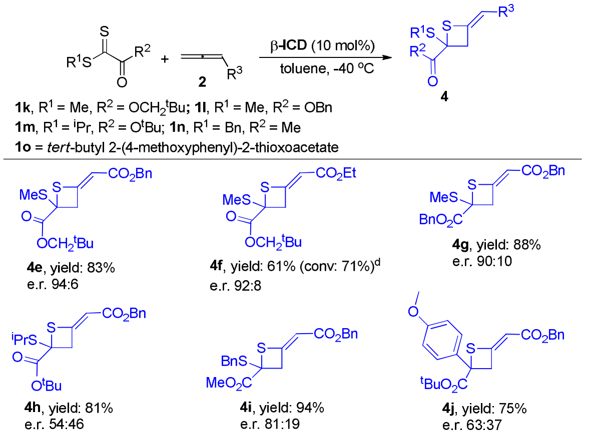
During the further exploration, we found that this [2+2] cycloaddition was not only catalyst-dependent but also substrate-dependent. When 2-thioxoacetates were employed as substrates, thietanes were the exclusive products no matter what kinds of nucleophilic amine catalysts were used. In terms of controlling the enantioselectivity in this [2+2] cyclization reaction, β-ICD was better than **C3** in this case. After simple examination, the optimal reaction conditions had been identified to carry out the reaction in toluene at -40 °C for 24 h using 10 mol% of β-ICD as the catalyst. As for the reaction of neopentyl 2-(methylthio)-2-thioxoacetate **1l** with benzyl buta-2,3-dienoate and ethyl buta-2,3-dienoate, the reactions proceeded smoothly to afford the corresponding products **4e** and **4f** in good e. r. values (Table 4). The enantioselectivity of this [2+2] cyclization was sensitive to the substituent linked to sulfur atom and product **4h** was obtained in 54:46 e. r. value. Changing neopentyl ester group to benzyl, and methyl ester group, the corresponding products **4g** and **4i** were obtained in good yields and good e. r. value. Notably, thioketone was also applicable to this novel [2+2] cyclization reaction, affording the desired product **4j** in good yield albeit with moderate e. r. value (Table 4).

Table 3. Substrate Scope for **C3**-catalyzed Asymmetric [2+2] Cycloadditions between Allenoates and Dithioesters.[a,b,c,d]



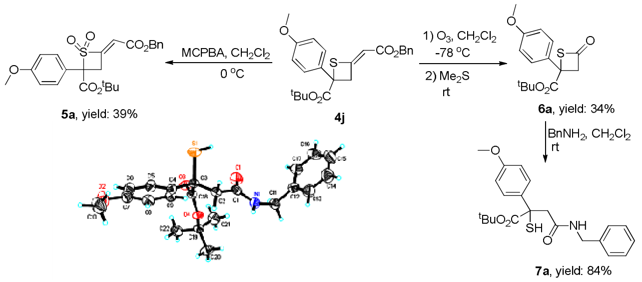
[a] Dithioester **1** (0.2 mmol), allenoate **2a** (0.2 mmol), and **C3** (0.02 mmol) were stirred in 2 mL of toluene at rt. [b] Isolated yields after chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis. [e] 50% of dithioester **1i** was recovered.

Table 4. Substrate Scope for β-ICD-catalyzed Asymmetric [2+2] Cycloadditions between Allenoates and 2-thioxoacetates.[a,b,c]

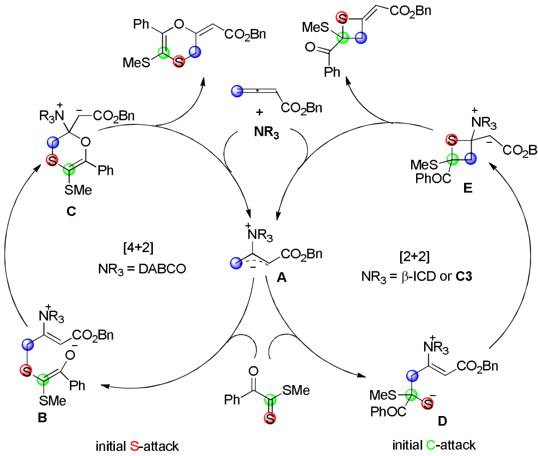


[a] Dithioester **1** (0.2 mmol), allenoate **2a** (0.2 mmol), and β-**ICD** (0.02 mmol) were stirred in 2 mL of toluene at rt. [b] Isolated yields after chromatography. [c] Determined by HPLC analysis. [d] 29% of dithioester **1k** was recovered.

To illustrate the synthetic utility of these obtained products, we further developed some transformations of [2+2] cycloadducts. Treating **4j** with MCPBA in CH_2Cl_2 gave sulfone **5a** in 39% yield. Ozonation of **4j** afforded β-thiolactone **6a** at -78 °C in 34% yield, which underwent ring-opening with phenylmethanamine to generate product **7a**. The structure of **7a** has been identified by X-ray diffraction and the CIF data are presented in the ESI.[17]

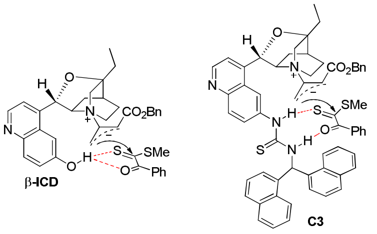


Scheme 2. The Transformations of Thietane **4j**



Scheme 3. Proposed Mechanism

A plausible mechanism is depicted in Scheme 3 to account for the selective control. The [4+2] and [2+2] cyclization reactions are initiated by the formation of zwitterionic intermediate **A** via the nucleophilic addition of amine to allenoate. When amine is DABCO, the thiophilic attack of **A** to the sulfur atom of the thiocarbonyl group in **1** generates intermediate **B**. The subsequent cyclization delivers product **3a** along with the liberation of the catalyst. Based on this mechanism, the reaction of dithioesters bearing electron-deficient R^2 group with allenoate is favored because the negative charge in intermediate **B** can be stabilized by delocalization. This is why they have better chemoselectivity (Table 2, entries 1 and 4). When amine catalyst is **C3** or β-ICD, the nucleophilic attack of zwitterionic intermediate **A** to the carbon atom of thiocarbonyl group in **1** is preferred, perhaps due to that the hydrogen bonding interaction between catalyst with its hydrogen bonding donor and substrate leads to the chemoselective [2+2] exceeding over [4+2] cycloaddition (Scheme 4).[18] Thus, the C-S bond is formed and the catalyst is released to give product **4a**.



Scheme 4. Proposed Hydrogen Bonding Interaction Mode

In summary, we have developed a novel amine-catalyzed tunable cycloadditions between allenoates and dithioesters, providing a divergent synthesis of 2,3-dihydro-1,4-oxathiines and enantioenriched thietanes. Through this finding, we can realize that dithioesters with a vicinal electron-withdrawing group can react not only like a Michael acceptor but also as a ketone or imine. The exploration of novel catalyst to further improving enantioselectivity of [2+2] cycloaddition between allenoates and dithioesters are underway in our laboratory.

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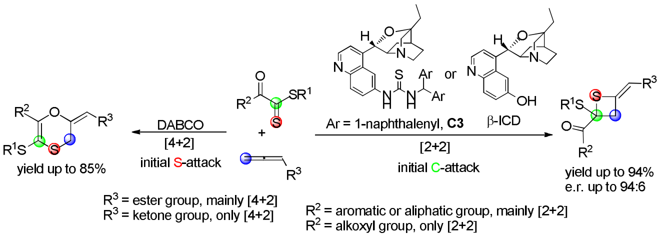
Amine-catalyzed Tunable Reactions of Allenoates with Dithioesters: Formal [4+2] and [2+2] Cycloadditions for the Synthesis of 2,3-dihydro-1,4-oxathiines and Enantioenriched Thietanes



The chemoselective [4+2] vs [2+2] cycloaddition between allenoates and dithioesters has been developed on the basis of switching nucleophilic amine catalyst, offering a divergent synthesis of sulfur-containing heterocycles.

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