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Asymmetric Cyclopropanation of β,γ-Unsaturated α-Ketoesters with Stabilized Sulfur Ylides Catalyzed by C_2-Symmetric Ureas

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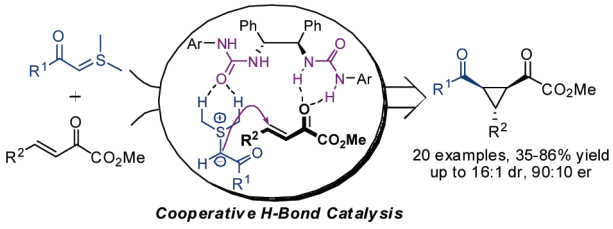
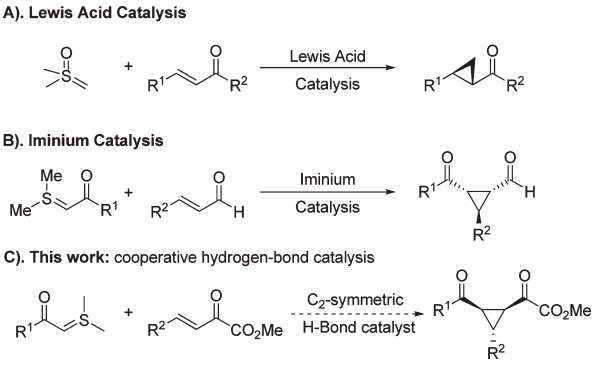


A novel organocatalytic asymmetric cyclopropanation of β,γ-unsaturated α-ketoesters with stabilized sulfur ylides using C_2-symmetric urea as a hydrogen-bond catalyst has been described. This reaction allows an efficient access to 1,2,3-trisubstituted cyclopropane derivatives in moderate to good yields with up to 16:1 dr and 90:10 er under mild reaction conditions. The mechanism study proved that the high stereoinduction originated from the cooperative effect of the hydrogen-bond catalyst.

The cyclopropane motif is a common structural subunit in many natural products and biologically active molecules and serves as a versatile and important building block in organic synthesis because of its unique combination of reactivity and structural properties.[1] Consequently, great research efforts have been directed toward the stereoselective construction of such three-membered carbocyclic rings over the last few decades.[2] Of the most important methods available, asymmetric cyclopropanation of electron-deficient olefins with ylides, pioneered by Corey in 1965,[3] is an attractive strategy. For example, Dai and Tang[4] have elegantly developed an enantioselective synthesis of vinylcyclopropanes using chiral telluronium and sulfonium ylides. However, catalytic asymmetric cyclopropanation of electron-deficient olefins with ylides is very rare. In this regard, the groups of Aggarwal[5] and Gaunt[6] first disclosed enantioselective cyclopropanations by the catalytic generation of chiral sulfonium and ammonium ylides. Recently, Shibasaki[7] successfully developed a La−Li (biphenyldiolate)$_3$/NaI complex-promoted asymmetric cyclopropanation of enones with dimethyloxosulfonium methylide (Scheme 1A). Notably, MacMillan ingeniously achieved a highly enantioselective organocatalytic cyclopropanation of α,β-unsaturated aldehydes with stabilized sulfonium ylides based on iminium catalysis and directed electrostatic activation by the use of 2-carboxylic acid dihydroindole as the catalyst (Scheme 1B).[8,9] Despite advances, the further development of efficient and practical organocatalytic systems[10]

SCHEME 1. Catalytic Asymmetric Cyclopropanation of Electron-Deficient Olefins with Sulfur Ylides



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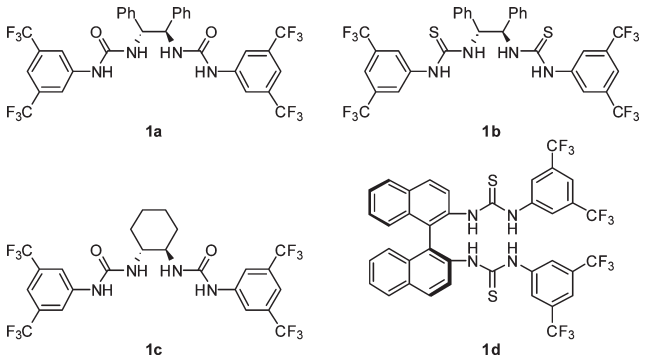


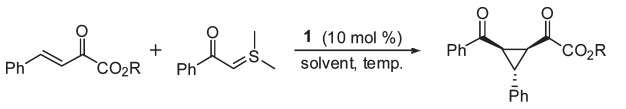
FIGURE 1. C_2-Symmetric hydrogen-bond catalysts employed in this study.

for the synthesis of optically active cyclopropanes with functional diversity is still highly desirable.[11]

As part of our ongoing program on carbon- and heterocycle-oriented methodology development based on sulfur ylides,[12] we recently disclosed highly chemo- and stereoselective [4 + 1] cycloaddition/rearrangement of nitroolefins,[12a] [4 + 1]/[3 + 2] cycloaddition cascade of alkene-tethered nitroolefins,[12b] and [4 + 1] cycloaddition of α,β-unsaturated imines, providing a variety of nitrogen-containing heterocycles.[12c] Inspired by these achievements, we describe herein the first example of hydrogen-bond catalyzed cyclopropanation of β,γ-unsaturated α-ketoesters with stabilized sulfur ylides (Scheme 1, C),[13,14] the products of which can be readily transformed into the corresponding amino acids or α-hydroxy acids.[15]

Initially, we investigated the possible cyclopropanation reaction between β,γ-unsaturated α-ketoester **2a** and sulfur ylide **3a** with four common and readily available C_2-symmetric hydrogen-bond catalysts (Figure 1).[16] As revealed in Table 1, all of these catalysts can efficiently promote the desired cycloaddition reactions at 10 mol % catalyst loading in toluene, giving the corresponding cyclopropane **4aa** with variable enantioselectivity (Table 1, entries 1−4). Initial catalyst screening indicated that urea **1a** displayed the highest catalytic activity in terms of reaction efficiency (77% isolated yield) and enantioselectivity (80:20 er) (Table 1, entry 1). With the use of **1a**, we then simply examined a series of solvents and revealed that toluene was the optimal reaction media

TABLE 1. Condition Optimization for the Asymmetric Cyclopropanation between β,γ-Unsaturated α-Ketoesters and Sulfur Ylide 3a[a]

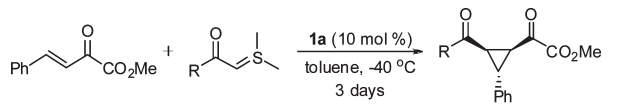


2 3a 4

entry	cat.	solvent	R	temp (°C)	yield[b] (%)	er[c]
1	**1a**	toluene	Me	0	77	80:20
2	**1b**	toluene	Me	0	27	75:25
3	**1c**	toluene	Me	0	53	80:20
4	**1d**	toluene	Me	0	50	54:46
5	**1a**	xylenes	Me	0	35	70:30
6	**1a**	THF	Me	0	45	53:47
7	**1a**	Et_2O	Me	0	61	60:40
8	**1a**	CH_2Cl_2	Me	0	27	53:47
9	**1a**	MeOH	Me	0	46	50:50
10	**1a**	toluene	Et	0	48	73:27
11	**1a**	toluene	^{i}Pr	0	53	72:28
12	**1a**	toluene	Me	−40	81	85:15

[a]Experimental conditions: a mixture of **2** (0.4 mmol), **3a** (0.44 mmol), and **1** (10 mol %) in solvent (2.0 mL) was stirred at the indicated temperature. [b]Isolated yield of the pure diastereoisomer **4**. [c]Determined by chiral HPLC analysis.

TABLE 2. Asymmetric Cyclopropanations of β,γ-Unsaturated α-Ketoester 2a with Sulfur Ylides 3a−k[a]



2a 3a-k 4aa-ak

entry	R		yield[b] (%)	dr[c]	er[d]
1	Ph (**3a**)	**4aa**	81	8:1	85:15
2	*p*-$MeOC_6H_4$ (**3b**)	**4ab**	85	12:1	78:22
3	*p*-MeC_6H_4 (**3c**)	**4ac**	85	8:1	81:19
4	*p*-FC_6H_4 (**3d**)	**4ad**	73	10:1	87:13
5	*p*-ClC_6H_4 (**3e**)	**4ae**	74	13:1	84:16
6	*p*-BrC_6H_4 (**3f**)	**4af**	86	12:1	83:17
7	*m*-BrC_6H_4 (**3g**)	**4ag**	60	10:1	77:23
8	*o*-$MeOC_6H_4$ (**3h**)	**4ah**	54	5:1	71:29
9	2-Thioenyl (**3i**)	**4ai**	61	4:1	87:13
10	PhCH=CH (**3j**)	**4aj**	37	5:1	78:22
11	$PhCH_2CH_2$ (**3k**)	**4ak**	85	10:1	72:28
12[e]	*p*-ClC_6H_4 (**3e**)	**4ae**	79	12:1	90:10

[a]Experimental conditions: a mixture of **2** (0.4 mmol), **3** (0.44 mmol), and **1a** (10 mol %) in toluene (2.0 mL) was stirred at −40 °C for 3 days. [b]Isolated yield of the pure diastereoisomer **4**. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis. [e]See the Supporting Information for details.

(Table 1, entries 5−9 vs entry 1). Further tuning of the steric hindrance of the ester moiety of β,γ-unsaturated α-ketoester led to no positive effect on the enantioselectivity (Table 1, entries 10 and 11). Finally, it was found that lowering the reaction temperature to −40 °C increased the enantiomeric ratio to 85:15 (Table 1, entry 12).

With the optimal conditions in hand (Table 1, entry 12, 10 mol % of urea **1a** in toluene at −40 °C), we first investigated the substrate scope for this asymmetric cyclopropanation by employing a variety of sulfur ylides. As summarized in Table 2, various sulfur ylides proved to be suitable for this catalytic asymmetric cyclization reaction. For example, both electron-donating and electron-withdrawing substituents in the benzene

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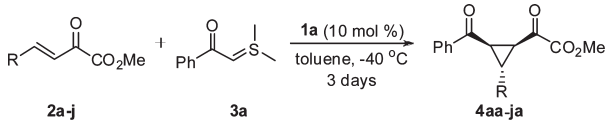
TABLE 3. Asymmetric Cyclopropanation of Sulfur Ylide 3a with Various β,γ-Unsaturated α-Ketoesters 2a−j[a]



2a-j 3a 4aa-ja

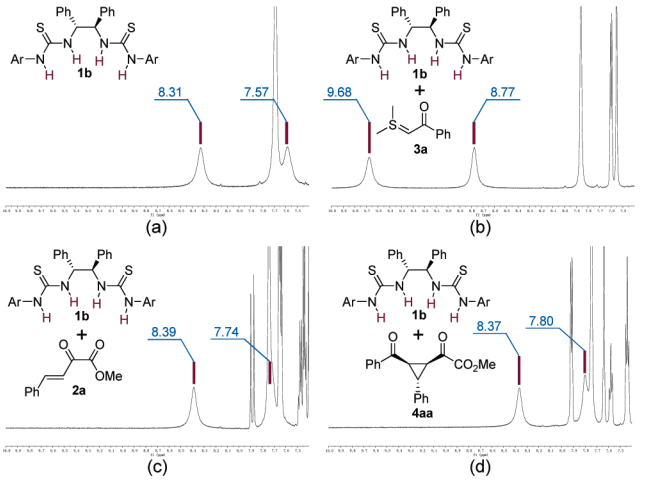
entry	R		yield[b] (%)	dr[c]	er[d]
1	Ph (**2a**)	**4aa**	81	8:1	85:15
2	*p*-MeOC$_6$H$_4$ (**2b**)	**4ba**	54	16:1	80:20
3	*p*-MeC$_6$H$_4$ (**2c**)	**4ca**	61	9:1	83:17
4	*p*-FC$_6$H$_4$ (**2d**)	**4da**	55	7:1	83:17
5	*p*-ClC$_6$H$_4$ (**2e**)	**4ea**	57	7:1	81:19
6	*p*-BrC$_6$H$_4$ (**2f**)	**4fa**	52	7:1	80:20
7	*m*-BrC$_6$H$_4$ (**2g**)	**4ga**	49	10:1	77:23
8	*o*-FC$_6$H$_4$ (**2h**)	**4ha**	56	5:1	81:19
9	*o*-ClC$_6$H$_4$ (**2i**)	**4ia**	58	9:1	85:15
10	PhCH=CH (**2j**)	**4ja**	35	2:1	90:10

[a]Experimental conditions: a mixture of **2** (0.4 mmol), **3a** (0.44 mmol), and **1a** (10 mol %) in toluene (2.0 mL) was stirred at −40 °C for 3 days. [b]Isolated yield of the pure diastereoisomer **4**. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis.

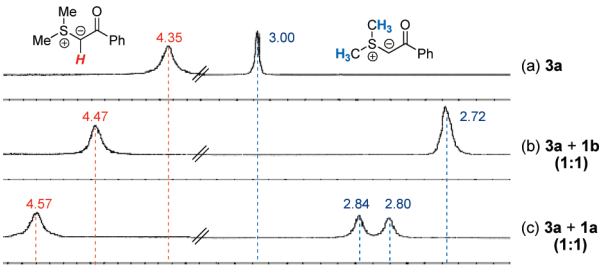
ring of sulfur ylide **3a**−**h** are well tolerated, and the corresponding products were obtained in moderate to good isolated yields (54−86%) and stereoselectivities (up to 13:1 dr, 87:13 er) (Table 2, entries 1−8). Introducing an electron-donating group (e.g., methoxyl) on the *ortho*-position of the aromatic ring led to somewhat decreased yield and diastereoselectivity (Table 2, entry 8). Note that the heterocycle-substituted sulfur ylide can also participate in this cyclization to give the desired product in good yield with 4:1 dr and 87:13 er (Table 2, entry 9). A vinyl-type group was also tolerated, albeit with diminished yield (Table 2, entry 10). Importantly, the reaction with alkyl-substituted sulfur ylide, such as **3k**, proceeded successfully to give cyclopropane **4ak** in 85% yield with 10:1 dr and 72:28 er (Table 2, entry 11). Notably, each of the products **4** can be easily separated by column chromatography on silica gel to obtain the major diastereoisomer as a pure compound. To demonstrate preparative utility, the reaction of **3e** and **2a** was performed on a larger scale (2.0 mmol vs 0.40 mmol). As expected, the reaction afforded the corresponding cyclopropane **4ae** in 79% isolated yield with good stereoselectivities (Table 2, entry 12).

Significantly, structural variation in the β,γ-unsaturated α-ketoester components can also be realized. As shown in Table 3, various electron-poor and -rich β,γ-unsaturated α-ketoesters with different substitution patterns on the aromatic ring reacted smoothly with sulfur ylide **3a** under optimal conditions, affording the corresponding cyclopropanes **4aa**−**ia** in high yields with high diastereo- (up to 16:1 dr) and enantioselectivities (up to 85:15 er) (Table 3, entries 1−9). Vinyl-subsituted β,γ-unsaturated α-ketoester, such as **2j**, can also be successfully employed in this transformation, and high er (90:10) was obtained, albeit with moderate yield and dr (35% yield, 2:1 dr) (Table 3, entry 10). The products **4aa**−**ak** and **4ba**−**4ja** were fully characterized by ^{1}H NMR and ^{13}C NMR, as well as HRMS. Furthermore, the absolute configuration of **4af** was unambiguously determined to be (1*S*,2*R*,3*R*) by X-ray analysis.[17]

SCHEME 2. Variation of Chemical Shifts of N−H of Thiourea 1b in Different Combinations (in $CDCl_3$, for b−d: donor/acceptor = 1:1)



SCHEME 3. Variation of Chemical Shifts of C−H of Sulfur Ylide 3a upon Combination with Catalysts (in $CDCl_3$)



To gain insight into the mechanism of the asymmetric cyclopropanation, we carried out a series of ^{1}H NMR spectroscopic studies with catalysts **1a** and **1b**, and the representative results are shown in Schemes 2 and 3.[18] It was demonstrated that two reaction components and the product have a substantial effect on the chemical shift of N−H in catalysts, and the H-bond interaction between sulfur ylide **3a** and **1b** was the strongest (Scheme 2b, $\Delta\delta$ 1.37 ppm; 1.20 ppm). Moreover, when the sulfur ylide **3a** was mixed with thiourea **1b** and urea **1a**, respectively, in $CDCl_3$, urea **1a** resulted in a remarkable change in chemical shift of C−H of ylide **3a**, which indicated a stronger H-bond interaction between urea **1a** and sulfur ylide **3a** (Scheme 3c: $\Delta\delta$ 0.22 ppm). Consequently, the hydrogen-bond catalyst urea **1a** was believed to provide a multi-hydrogen-bond cooperative substrate activation.[14]

Based on the above observations and the X-ray structure of the product **4af** (Figure 2), we proposed a possible pathway to account for the observed stereoinduction. As depicted in Scheme 4, catalyst **1a** interacted with ylide **3a** to form the complex **A** through a strong hydrogen-bond effect. Then, the resulting complex **A** incorporated with β,γ-unsaturated

(17) CCDC 776429 for product **4af** contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk / data_request/cif.

(18) In the ^{1}H NMR experiments, we used thiourea **1b** other than urea **1a** because of the poor solubility of urea **1a** in $CDCl_3$. Interestingly, we found that the mixture of urea **1a** and ylide **3a** was completely dissolved in $CDCl_3$ possibly due to the strong H-bond interaction. Please see more details in the Supporting Information.

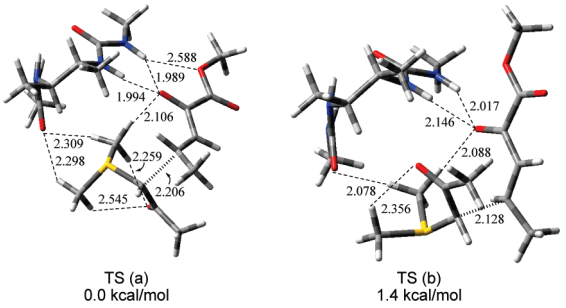
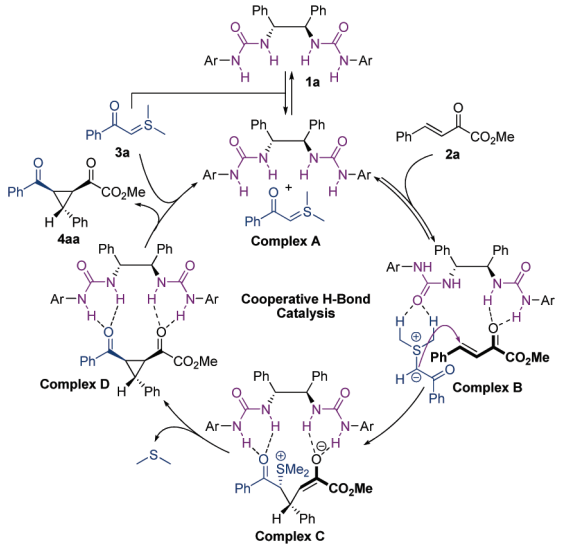


FIGURE 2. Optimized structure and free energy gap of the transition states.

SCHEME 4. Proposed Catalytic Pathway



α-ketoester **2a** to give a ternary complex **B**, wherein the hydrogen bonds directed the reactants in the proper positions and induced the observed facial selectivities in intermediate **C**.[14,16] Finally, the intermediate **C** underwent an intramolecular S_N2 displacement to afford the desired propane **4aa** with release of the urea **1a** for the next catalytic cycle. Note that the prediction of possible interaction in complex **B** was in agreement with the NMR studies and DFT calculation (Figure 2).[19]

In conclusion, we have developed a catalytic asymmetric cyclopropanation of *β*,*γ*-unsaturated α-ketoesters with sulfur ylides by cooperative hydrogen-bond catalysis. The process provided a complementary method to previously documented Lewis acid or chiral amine catalyzed asymmetric cyclopropanation.[7,8] Although the stereoselectivity awaits further improvement, the current methodology provide a new strategy for catalytic asymmetric cyclopropanation reactions. Additional mechanistic studies and extension of this methodology to more functionalized substrates are now ongoing in our research group.

(19) See the Supporting Information for details.

Experimental Section

General Procedure for Asymmetric Cyclopropanation between *β*,*γ*-Unsaturated α-Ketoesters and Stabilized Sulfur Ylides. *β*,*γ*-Unsaturated α-ketoester **2a** (76.1 mg, 0.40 mmol) and catalyst **1a** (28.9 mg, 0.04 mmol) were mixed in dry toluene (2.0 mL). After the mixture was stirred at −40 °C for 0.5 h, sulfur ylide **3a** (79.3 mg, 0.44 mmol) was introduced directly. The reaction mixture was stirred at −40 °C for 3 days. After complete consumption of the *β*,*γ*-unsaturated α-ketoester **2a** (as monitored by TLC), the mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl ether (5:1−3:1)) to give the corresponding pure product **4aa** in 81% yield as white solid. The diastereoisomer ratio (8:1) was directly determined by ^{1}H NMR of the reaction mixture. The enantiomeric ratio (85:15) was determined by chiral HPLC analysis (Daicel Chirapak OD-H, hexane/2-propanol 90/10, flow rate 1.0 mL/min, *T* 25 °C, 254 nm, t_R 21.71 min (major), t_R 19.29 min (minor)): $[\alpha]^{19}_D$ +67.65 (*c* 2.5, $CHCl_3$).

Methyl 2-(2-benzoyl-3-phenylcyclopropyl)-2-oxoacetate (4aa): ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.96 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 2H), 3.88 (s, 3H), 3.47−3.42 (m, 2H), 3.31 (dd, *J* = 8.7, 6.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 194.09, 188.50, 160.88, 137.32, 135.96, 133.67, 128.81, 128.66, 128.52, 127.43, 126.37, 53.06, 39.35, 34.73, 32.09; MS *m*/*z* 308.2 (M^+); HRMS *m*/*z* calcd for $C_{19}H_{17}O_4^+$ $[M + H]^+$ 309.1127, found 309.1111.

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Supporting Information Available: Full experimental details, spectroscopic data of **4**, CIF file for **4af**, HPLC spectra of **4**, and details of mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.