NHC-Catalyzed Enantioselective [2 + 2]and [2 + 2 + 2] Cycloadditions of Ketenes with Isothiocyanates

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The enantioselective *N*-heterocyclic carbene-catalyzed formal [2 + 2] and [2 + 2 + 2] cycloaddition of ketenes and isothiocyanates were developed. Reaction with *N*-aryl isothiocyanates at room temperature favors the [2 + 2] cycloaddition, while reaction with *N*-benzoyl isothiocyanates at -40 °C favors the [2 + 2 + 2] cycloaddition.

The cycloaddition reactions of ketenes are powerful tools for the construction of various cyclic compounds.^{1,2} During the past few years, we demonstrated that N-heterocyclic carbenes (NHCs)³ are efficient catalysts for cycloaddition reactions of ketenes with carbonyl compounds, imines, heterodienes, oxaziridines, carbon disulfide, and

N-sulfinylanilines.^{4,5} Because of their easy availability and diverse reactions, isothiocyanates are widely utilized, especially in the synthesis of heterocycles.^{6,7} In 1965, Winberg et al. reported the reaction of NHCs with isothiocyanates to form stable adducts.⁸ Recently, Cheng et al. have successfully developed this process for the synthesis of a

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wide range of heterocycles.⁹ Very recently, Yadav et al. reported the NHC-catalyzed [2 + 2] cycloaddition of isothiocyanates and nitroolefins.^{10,11} In this paper, we report an NHC-catalyzed enantioselective reaction of ketenes with isothiocyanates for the synthesis of 4-thioxo-2-azetidinones (thioxo- β -lactams), which are potential synthons for bioactive heterocycles,¹² such as sulfur-containing β -lactam antibiotics.¹³ Although 4-thioxo-2-azetidinones have been prepared from degradation of penicillin since 1976,¹⁴ to the best of our knowledge, the enantioselective synthesis of this key motif remains unrealized.

Initially, we found that the reaction of ketene **1a** and *N*phenyl isothiocyanate gave the desired 4-thioxo-2-azetidinone **3a** in 13% yield with 75% ee in the presence of NHC **A1**', generated freshly from NHC precursor **A1** and Cs_2CO_3 , at room temperature (Scheme 1). Encouraged by this result, several isothiocyanates were then screened. Reaction with *N-p*-chlorophenylisothiocyanates gave the desired product **4a** in 25% yield with 70% ee. The yield was increased to 69% albeit with 39% ee when *N-p*-nitrophenyl isothiocyanate was used. Reaction of *N*-benzoyl isothiocyanate gave no desired cycloadduct but a complex mixture.

Scheme 1. Screening of Isothiocyanates



The reaction of ketene **1a** and *N*-*p*-nitrophenyl isothiocyanate (**2c**) was optimized (Table 1). It is interesting that

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better yield and enantioselectivity were realized when the reaction was carried out in dilute solution (entries 1-5). Several NHC precursors A2-A5, derived from L-pyroglutamic acid were then tested for the reaction. NHC precursor A2 with an N-phenyl group led to a decreased yield with moderate enantioselectivity (entry 6), while NHC precursors A3-A4 with an N-benzyl group showed better enantioselectivity but decreased vield (entries 7 and 8). NHC precursor A5 with a free hydroxyl group afforded the cycloadduct 5a in 73% with 96% ee (entry 9). NHC precursor **B**, derived from chiral indanol, resulted in low vield and enantioselectivity (entry 10). The yield was improved when excess ketene (2.5 equiv) was used and added via a syringe pump (entries 11 and 12). Unexpectedly, a [2 + 2 + 2] cycloadduct 7a was observed, along with the normal [2 + 2] cycloadduct **5a**, when the reaction temperature was lowed to -10 or -40 °C (entries 13 and 14)





entry	precat.	DCM (x mL)	$T(^{\circ}\mathrm{C})$	yield ^{a} (%)	ee^b
1	A1	5	\mathbf{rt}	69	39
2	A1	2.5	rt	60	33
3	A1	10	rt	70	52
4	A1	15	rt	96	55
5	A1	20	\mathbf{rt}	91	57
6	A2	15	\mathbf{rt}	74	55
7	A3	15	\mathbf{rt}	75	85
8	A4	15	\mathbf{rt}	66	83
9	A5	15	\mathbf{rt}	73	96
10	В	15	\mathbf{rt}	31	-33
11^c	A5	15	\mathbf{rt}	76	96
$12^{c,d}$	A5	15	\mathbf{rt}	80	97
13	A5	15	-10	$60(6)^{e}$	$97 (96)^e$
14	A1	5	-40	$< 10 (18)^{e}$	$42(71)^{e}$

^{*a*} Isolated yield. ^{*b*} Deterninded by chiral HPLC. ^{*c*} Ketene **1a** was added via a syringe pump over 3 h. ^{*d*} 2.5 mmol of ketene **1a** was used. ^{*e*} Yield and ee of **7a** were showed in parentheses.

A variety of aryl(alkyl)ketenes were tested under the optimized conditions for the [2 + 2] cycloaddition (Table 2). Both aryl(alkyl)ketenes with electron-withdrawing groups (Ar = 4-Cl, 4-BrC₆H₄) and with electron-donating groups (Ar = 4-Me, 4-MeOC₆H₄) worked well to give the corresponding 4-thioxo-2-azetidinones **5** in good yields with high enantioselectivities (entries 2–5). The ketene **1f** with an *m*-chlorophenyl group worked well for the reaction, but ketene **1g** with an *o*-chlorophenyl group did not (entries 6 and 7). The ketenes with methyl, *n*-propyl, and *n*-butyl groups all worked well, affording the desired cycloadducts in high yields with high enantioselectivities (entries 8-10). However, ketene **1k** with isopropyl group gave no cycloadduct under the current reaction conditions (entry 11).

Table 2. NHC-Catalyzed [2 + 2] Cycloaddition

0 C	+ C	precat Cs ₂ C	A5 (12 mol) 0 ₃ (10 mol 9	%) O		
Ar	R PNP ^N	DC	M (15 mL),	rt R	s	
(2.5 mi 1	mol) (1.0 mmol) 2c			PNP = 4-1 5	NO ₂ C ₆ H ₄	
entry	1 (Ar, R)	5	time (h)	yield ^{a} (%)	ee ^b (%)	
1	1a, Ph, Et	5a	21	80	97	
2	1b, 4-ClC ₆ H ₄ , Et	$\mathbf{5b}$	21	75	97	
3	1c, 4 -BrC ₆ H ₄ , Et	5c	27	62	95	
4	1d, 4-MeC ₆ H ₄ , Et	5d	22	65	93	
5	1e, 4 -MeOC ₆ H ₄ , Et	5e	141	63	93	
6	1f, 3-ClC ₆ H ₄ , Et	5f	39	70	96	
7	1g, 2-ClC ₆ H ₄ , Et	5g	61	NR	/	
8	1 h , Ph, Me	5h	15	78	92	
9	1i, Ph, <i>n</i> -Pr	5 i	20	81	93	
10	1 j, Ph, <i>n</i> -Bu	5j	10	85	92	
11	1k , 4-ClC ₆ H ₄ , <i>i</i> -Pr	5k	125	NR	/	
^a Iso	plated yield. b Determin	ed by l	HPLC. NR	= no reactio	n.	

We then turned our attention to the possible [2 + 2 + 2]cycloaddition (Table 3). It is interesting that although the reaction with N-benzoylisothiocyanate gave a complex mixture at room temperature, the corresponding [2 + 2 + 2]cycloadduct 8a was isolated in 40% yield with 86% ee without the observation of [2 + 2] cycloadduct when the reaction was carried out at -10 °C (entries 1 and 2). Solvent screening revealed that no improvement was made in toluene or acetonitrile (entries 3 and 4). Reaction temperature (-10 to -60 °C) and dosage of the ketene had strong impact on the yield of the reactions (entries 5-8). A little excess of ketene (1a:2d = 2.5:1) and lowing the reaction temperature to -40 °C gave cycloadduct 8a in 60% yield with 83% ee (entry 7). Further experiments showed that concentration could also alter the yield of the reaction (entries 7, 9-10). Moderately concentrated solution ([1a] = 1.0 M) benefited the reaction, giving cycloadduct 8a in 72% yield with 85% ee (entry 9).

Several ketenes were then tested for the [2 + 2 + 2] cycloaddition reaction with *N*-benzoyl isothiocyanate, which showed similar scope as the [2 + 2] cycloaddition reaction with *N*-*p*-nitrophenyl isothiocyanate (Table 4). Both electron-withdrawing substituents and electron-donating substituents were tolerable for the aryl(alkyl)-ketenes (entries 2–5). However, ketene **1g** with a 2-chlorophenyl group gave no cycloadduct (entry 6). The ketenes with methyl, *n*-propyl, and *n*-butyl groups all worked well, but ketene **1k** with isopropyl group did not(entries 7–10).

Table 3. Condition Optimization of the [2 + 2 + 2] Cycloaddition



entry	1a:2d	solvent	$T(^{\circ}\mathrm{C})$	yield ^{a} (%)	ee^{b} (%)
1	1.5:1	DCM	rt	mixture	/
2	1.5:1	DCM	$^{-10}$	40	86
3	1.5:1	toluene	-10	21	87
4	1.5:1	CH_3CN	-10	15	46
5	1:1.5	DCM	$^{-10}$	21	77
6	2.5:1	DCM	$^{-10}$	40	73
7	2.5:1	DCM	-40	60	83
8	2.5:1	DCM	-60	39	84
9^c	2.5:1	DCM	-40	72	85
10^d	2.5:1	DCM	-40	64	83

^{*a*} Isolated yield. ^{*b*} Determined by HPLC. ^{*c*} 2.5 mL of DCM was used. ^{*d*} 1.5 mL of DCM was used.

Table 4. NHC-Catalyzed	[2 + 2 +	2] Cycload	ldition
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O C C (2.5 mi (2.5 mi 1a	+ `R mol)	S C Bz [^] N (1.0 mmol) 2d	precat. Cs ₂ CC DCM (2	A1 (12 mol ⁰ D ₃ (10 mol % 2.5 mL), -40	%)) °C Ar R N 8	Ar R S Bz
entry	1 (A	r, R)	8	time (h)	yield ^{a} (%)	$\mathrm{ee}^{b}\left(\% ight)$
1	1a , Ph, E	t	8a	45	72	86
2	1b, 4-ClC	$_{6}\mathrm{H}_{4},\mathrm{Et}$	8b	53	62	75
3	1d, 4-Me	C_6H_4 , Et	8d	41	71	78
4	1e, 4 -MeOC ₆ H ₄ , Et		8e	78	54	67
5^c	1f , 3-ClC ₆ H ₄ , Et		8f	39	50	61
6^d	1g, 2-ClC ₆ H ₄ , Et		8g	50	NR	/
7	1h, Ph, Me		8h	38	60	77
8	1i, Ph, <i>n</i> -Pr		8i	51	65	81
9	1j , Ph, <i>n</i> -	Bu	8j	31	66	79
10^d	1k, 4-ClC	C_6H_4 , <i>i</i> -Pr	8k	113	NR	/

^{*a*} Isolated yield. ^{*b*} Determined by HPLC. ^{*c*} Reaction was carried out at -10 °C. ^{*d*} No reaction occurred at -40 °C or room temperature.

Both the structures of [2 + 2] cycloadduct **5h** and [2 + 2 + 2] cycloadduct **7a** were unambiguously established by X-ray analysis of their crystals (Figures S1 and S3, Supporting Information).¹⁵

The resulted highly functionalized cycloadducts offer many opportunity of chemical transformations. For example, alcoholysis of the cycloadduct **5a** gave the ring-opening

⁽¹⁵⁾ See the Supporting Information for details.





compound 9 in 78% yield without apparent erosion of enantiopurity (eq 1).



The plausible reaction pathways are depicted in Scheme 2. The addition of NHC to ketenes generates intermediate A, which reacts with isothiocyanate to give intermediate **B**. Intermediate **B** may collapse via an intramolecular *N*-addition to azolium acyl to furnish [2 + 2] cycloadducts **5** and regenerates NHC (pathway a). However, when the isothiocyanate with *N*-benzoyl is employed the intermediate **B** is stabilized with resonant structure **B3**, which facilitates the *S*-addition to the second molecule of ketene to generate intermediate **C** at low temperature (pathway b). Intermediate **C** collapses via an intramolecular *O*-addition to azolium acyl to furnish [2 + 2 + 2] cycloadducts **8** and regenerates NHC. Control experiments revealed that [2 + 2] cycloadduct in the presence of ketene under the reaction condition of [2 + 2 + 2] cycloaddition.¹⁵

In summary, the enantioselective N-heterocyclic carbene-catalyzed formal [2 + 2] and [2 + 2 + 2] cycloadditions of ketenes and isothiocyanates were developed. Reaction with N-arylisothiocyanates at room temperature favors the [2 + 2] cycloaddition to give the 4-thioxo-2-azetidinones (thioxo- β -lactams) in good yields with high enantioselectivities, while reaction with N-benzoyl isothiocyanates at -40 °C favors the [2 + 2 + 2] cycloaddition to give the corresponding 1,3-oxathian-6-ones in good yields with good enantioselectivities. The resulted optically active cycloadducts are potentially useful for the synthesis of sulfurcontaining heterocycles, particularly the β -lactam antiobiotics.

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Supporting Information Available. Experimental procedures, compound characterization and X-ray data for cycloadducts **5h** and **7a** (CIF). This material is available free of charge via the Internet at http://pubs.acs. org.