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

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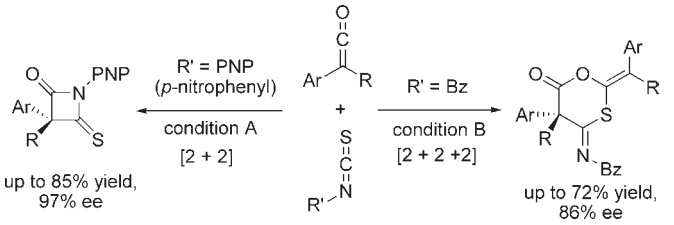
ABSTRACT



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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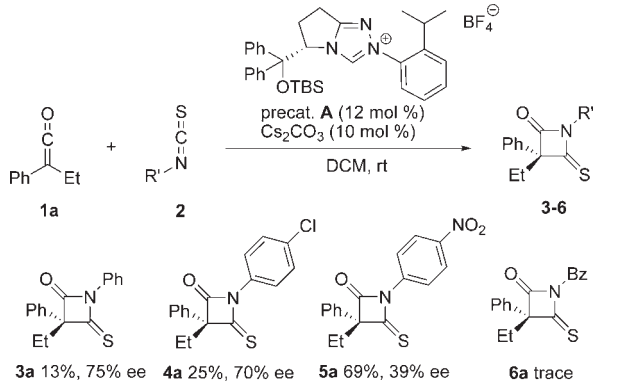
wide range of heterocycles.[9] Very recently, Yadav et al. reported the NHC-catalyzed [2 + 2] cycloaddition of isothiocyanates and nitroolefins.[10,11] In this paper, we report an NHC-catalyzed enantioselective reaction of ketenes with isothiocyanates for the synthesis of 4-thioxo-2-azetidinones (thioxo-β-lactams), 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.

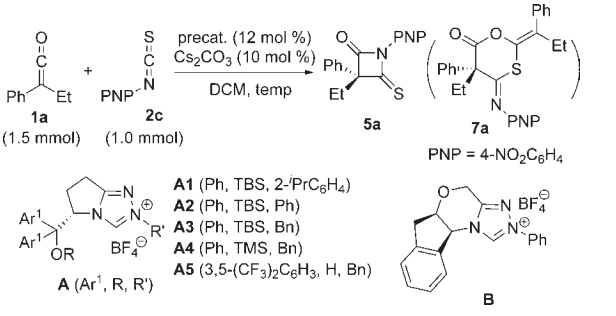
Initially, we found that the reaction of ketene **1a** and *N*-phenyl isothiocyanate gave the desired 4-thioxo-2-azetidinone **3a** in 13% yield with 75% ee in the presence of NHC **A1′**, generated freshly from NHC precursor **A1** and Cs_2CO_3, at room temperature (Scheme 1). Encouraged by this result, 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 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 yield (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 yield 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)

Table 1. Condition Optimization of [2 + 2] Cycloaddition



entry	precat.	DCM (x mL)	T (°C)	yield[a] (%)	ee[b]
1	**A1**	5	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	rt	91	57
6	**A2**	15	rt	74	55
7	**A3**	15	rt	75	85
8	**A4**	15	rt	66	83
9	**A5**	15	rt	73	96
10	**B**	15	rt	31	−33
11[c]	**A5**	15	rt	76	96
12[c,d]	**A5**	15	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-BrC_6H_4) and with electron-donating groups (Ar = 4-Me, 4-MeOC_6H_4) 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

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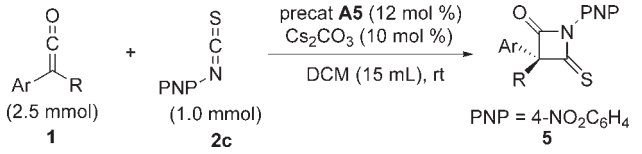
ketene **1g** with an *o*-chlorophenyl group did not (entries 6 and 7). The ketenes with methyl, *n*-propyl, and *n*-butyl groups all worked well, affording the desired cycloadducts in high yields with high enantioselectivities (entries 8–10). However, ketene **1k** with isopropyl group gave no cycloadduct under the current reaction conditions (entry 11).

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



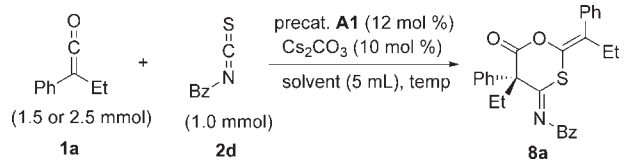
entry	**1** (Ar, R)	**5**	time (h)	yield[a] (%)	ee[b] (%)
1	**1a**, Ph, Et	**5a**	21	80	97
2	**1b**, 4-ClC_6H_4, Et	**5b**	21	75	97
3	**1c**, 4-BrC_6H_4, Et	**5c**	27	62	95
4	**1d**, 4-MeC_6H_4, Et	**5d**	22	65	93
5	**1e**, 4-$MeOC_6H_4$, Et	**5e**	141	63	93
6	**1f**, 3-ClC_6H_4, Et	**5f**	39	70	96
7	**1g**, 2-ClC_6H_4, Et	**5g**	61	NR	/
8	**1h**, Ph, Me	**5h**	15	78	92
9	**1i**, Ph, *n*-Pr	**5i**	20	81	93
10	**1j**, Ph, *n*-Bu	**5j**	10	85	92
11	**1k**, 4-ClC_6H_4, *i*-Pr	**5k**	125	NR	/

[a] Isolated yield. [b] Determined by HPLC. NR = no reaction.

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).

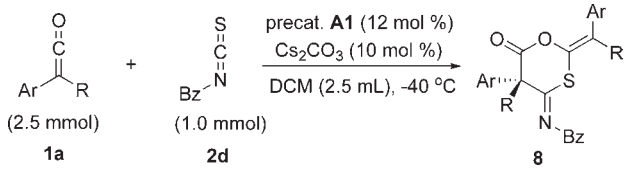
Table 3. Condition Optimization of the [2 + 2 + 2] Cycloaddition



entry	**1a**:**2d**	solvent	*T* (°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] Cycloaddition



entry	**1** (Ar, R)	**8**	time (h)	yield[a] (%)	ee[b] (%)
1	**1a**, Ph, Et	**8a**	45	72	86
2	**1b**, 4-ClC_6H_4, Et	**8b**	53	62	75
3	**1d**, 4-MeC_6H_4, Et	**8d**	41	71	78
4	**1e**, 4-$MeOC_6H_4$, Et	**8e**	78	54	67
5[c]	**1f**, 3-ClC_6H_4, Et	**8f**	39	50	61
6[d]	**1g**, 2-ClC_6H_4, Et	**8g**	50	NR	/
7	**1h**, Ph, Me	**8h**	38	60	77
8	**1i**, Ph, *n*-Pr	**8i**	51	65	81
9	**1j**, Ph, *n*-Bu	**8j**	31	66	79
10[d]	**1k**, 4-ClC_6H_4, *i*-Pr	**8k**	113	NR	/

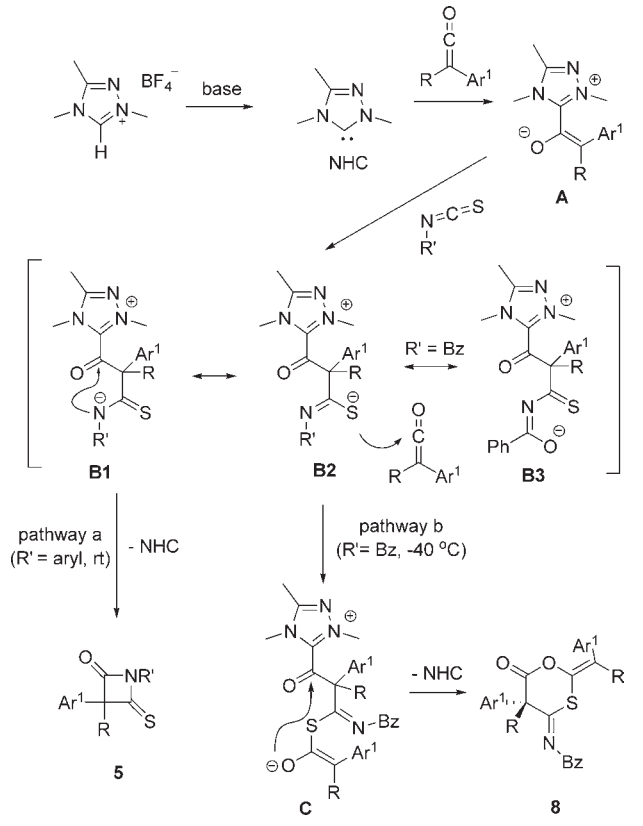
[a] Isolated yield. [b] Determined by HPLC. [c] Reaction was carried out at −10 °C. [d] No reaction occurred at −40 °C or room temperature.

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]

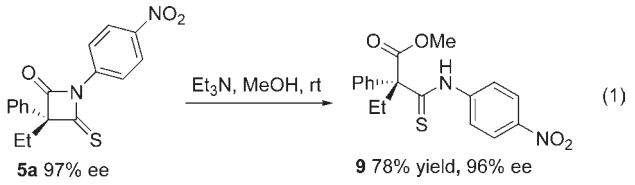
The resulted highly functionalized cycloadducts offer many opportunity of chemical transformations. For example, alcoholysis of the cycloadduct **5a** gave the ring-opening

(15) See the Supporting Information for details.

Scheme 2. Plausible Reaction Pathways



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



(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 could not be transformed to [2 + 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 sulfur-containing 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.