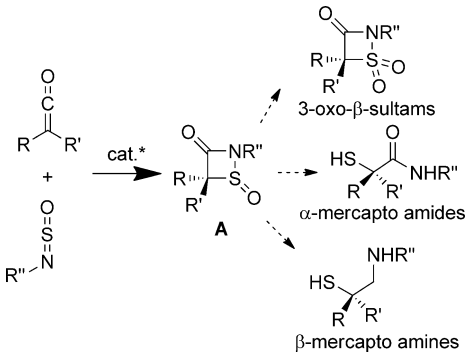
Asymmetric Catalysis

DOI: 10.1002/ange.201102488

N-Heterocyclic Carbene Catalysis: Enantioselective Formal [2+2] Cycloaddition of Ketenes and *N*-Sulfinylanilines**

*Teng-Yue Jian, Lin He, Cen Tang, and Song Ye**

As analogues of both β-sultams and β-lactams, 3-oxo-β-sultams (1,2-thiazetidin-3-one 1,1-dioxides), are a novel class of four-membered heterocycles showing interesting biological activities.[1] However, to the best of our knowledge, there is no report for the enantioselective synthesis of these heterocycles.[1a] We envisioned that the 3-oxo-β-sultams could be easily synthesized by oxidation of the corresponding 1,2-thiazetidin-3-one 1-oxides (**A**),[2] which could be accessed from the [2+2] cycloaddition of ketenes with *N*-sulfinylamines (Scheme 1).



Scheme 1. Synthesis and applications of thiazetidinone oxide (**A**).

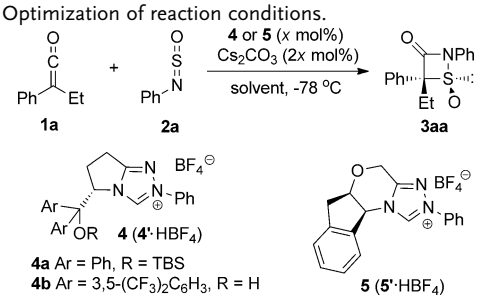
In addition, the cycloadduct **A** could also undergo a ring opening to give the α-mercapto acid derivatives and β-mercapto amines, which are both key structures of bioactive compounds[3] and highly useful chiral reagents or ligands for asymmetric synthesis.[4]

In the last several years, we successfully demonstrated that N-heterocyclic carbenes (NHCs)[5] are efficient catalysts for enantioselective reactions of ketenes,[6] including a series of formal [2+2], [3+2], and [4+2] cycloaddition reactions of ketenes with 2-oxoaldehydes,[7] activated ketones,[8] imines,[9] oxaziridines,[10] and heterodienes.[11] Herein we report an NHC-catalyzed enantioselective reaction of ketenes and *N*-sulfinylanilines to give chiral 1,2-thiazetidin-3-one 1-oxides.

After some initial attempts, we were happy to find that ethyl(phenyl)ketene (**1a**) and *N*-sulfinylaniline (**2a**) reacted in the presence of 10 mol% of the NHC **4a′**[10a,12] (generated from the triazolium salt **4a** derived from L-pyroglutamic acid in the presence of 20 mol% of Cs_2CO_3) to give the corresponding 1,2-thiazetidin-3-one 1-oxide (**3aa**) in 93% yield with 96% *ee* (Table 1, entry 1). The NHC **4b′**, having a free hydroxy group, also worked for the reaction but resulted in somewhat lower yield (entry 2). The NHC **5′**,[13] derived from aminoindanol, catalyzed the reaction to give the enantiomer of the cycloadduct in 95% yield with 99% *ee* (entry 3). No significant change in yield or enantioselectivity was observed when the catalyst loading was reduced to 5 mol% (entry 4). Although the yield decreased sharply to 36%, the excellent enantioselectivity was maintained when 2 mol% of the NHC was utilized (entry 5). Solvent screening with toluene or THF resulted in a small increase of the yield (entries 6 and 7).

A dramatic improvement in the yield was realized when 4 Å molecular sieves (M.S.) were added as the additive. The addition of M.S. may serve to remove trace amounts of water and thus reduce the hydrolysis of the ketene and *N*-sulfinylamine, thereby resulting in improvement of the yield of the cycloadduct. With the addition of M.S., both enantiomers of

Table 1: Optimization of reaction conditions.



Entry	**4** or **5** (*x* mol%)[a]	Solvent	**3aa**	Yield [%][b]	*ee* [%][c]
1	**4a** (10)	CH_2Cl_2	(+)-**3aa**	93	96
2	**4b** (10)	CH_2Cl_2	(+)-**3aa**	64	98
3	**5** (10)	CH_2Cl_2	(−)-**3aa**	95	99
4	**4a** (5)	CH_2Cl_2	(+)-**3aa**	89	98
5	**4a** (2)	CH_2Cl_2	(+)-**3aa**	36	98
6	**4a** (2)	toluene	(+)-**3aa**	62	99
7	**4a** (2)	THF	(+)-**3aa**	50	99
8[d]	**4a** (2)	CH_2Cl_2	(+)-**3aa**	95	99
9[d]	**4a** (1)	CH_2Cl_2	(+)-**3aa**	95	99
10[d]	**5** (1)	CH_2Cl_2	(−)-**3aa**	94	99

[a] The NHCs **4′** and **5′** were freshly generated from the precatalysts **4** and **5** (*x* mol%) in the presence of Cs_2CO_3 (2*x* mol%) at room temperature for 30 min, and then used immediately. [b] Yield of isolated product. [c] Determined by HPLC methods using a stationary phase. [d] 4 Å M.S. were added. TBS = *tert*-butyldimethylsilyl.

[*] T.-Y. Jian, Dr. L. He, C. Tang, Prof. Dr. S. Ye
Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences
Beijing 100190 (China)
E-mail: songye@iccas.ac.cn

[**] Financial support from the National Natural Science Foundation of China (No. 20872143, 20932008), the Ministry of Science and Technology of China (2011CB808600), and the Chinese Academy of Sciences is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201102488.

cycloadduct **3aa** could be obtained in very high yields with excellent enantioselectivities even when utilizing as little as 1 mol% of either **4a′** or **5′** as the catalyst (Table 1, entries 9 and 10).

With the optimized reaction conditions in hand, a variety of ketenes and *N*-sulfinylanilines were tested for the reaction (Table 2). Both aryl(ethyl)ketenes with electron-donating groups (4-Me, 4-$MeOC_6H_4$) and those with electron-withdrawing groups (4-Br, 4-ClC_6H_4) worked very well for the reactions catalyzed by either **4a′** or **5′**, thus affording the cycloadducts in very good yields with excellent enantioselectivities (entries 1–5). The reaction of 3-chlorophenyl(ethyl)ketene (**1f**) catalyzed by 1 mol% of **4a′** led to some decreased enantioselectivity, and 10 mol% of **4a′** is required for the reaction of 2-chlorophenyl(ethyl)ketene (**1g**) to achieve high enantioselectivity (entries 6 and 7). It is interesting that 1 mol% of **5′** worked well for the reactions of the ketenes **1f** and **1g** (entries 6 and 7); the lower loading of **5** may result from the smaller steric bulk of the NHC **5′** relative to **4a′**. Phenyl(alkyl)ketenes **1h**, **1i**, and **1j** with methyl, *n*-propyl, and *n*-butyl groups, respectively, worked very well (entries 8–10). Again, the sterically crowed ketene **1k** having an isobutyl group showed somewhat decreased enantioselectivity (entry 11). The reaction of diphenylketene (**1l**) catalyzed by **5′** gave the desired cycloadduct in 81% yield with 82% *ee*, whereas the reaction catalyzed by **4a′** resulted in very low yield and selectivity (entry 12). The cyclic ketene **1m** (cycloheptylidenemethanone) resulted in the desired cycloadduct in very good yield albeit with a very low *ee* value (entry 13).

Other *N*-sulfinylanilines, **2b–2e**, having both electron-donating (4-Me, 4-$MeOC_6H_4$) and electron-withdrawing groups (4-Cl, 4-FC_6H_4) worked as well as *N*-sulfinylaniline **2a** (Table 2, entries 14–17). In addition, the sulfinylanilines **2f–2h** having 2-substituted aryl groups (2-MeO, 2-Cl, 2-FC_6H_4) also worked very well, thus giving the cycloadducts in good yields with 91–99% *ee* (entries 18–20).

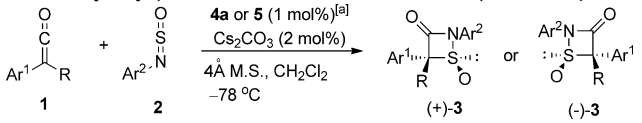
The relative and absolute structure of thiazetidinone oxide (−)-**3ha** was unambiguously established by X-ray analysis of its crystal.[14]

The highly functional cycloadducts **3** afford many possibilities for chemical transformations (Scheme 2). As expected, the 3-oxo-β-sultam **6aa** could be obtained in 95% yield with 98% *ee* by the oxidation of the cycloadduct **3aa**,[15] and alcoholysis of **6aa** gave the sulfate **7aa** in good yield (Scheme 2, steps a and b).[1e] Aminolysis of the cycloadduct **3aa** with pyrrolidine gave the sulfonamide **8aa** (Scheme 2, step c).[16] Reductive ring-opening with DIBAL-H afforded α-mercapto amides **9aa**, **9ha**, and **9ae** in good yields with excellent enantioselectivities at −78°C (Scheme 2, step d).[17] It is interesting that the 1,2-mercapto amine resulted in good yield as the reductive reaction was carried out at room temperature (Scheme 2, step e).

Although the noncatalytic [2+2] cycloaddition reaction of ketenes with sulfur dioxide,[18] sulfur diimides,[2c] or *N*-sulfinylanilines[2a,b] have been reported, we have not observed the noncatalytic background [2+2] cycloaddition reaction of ketenes and *N*-sulfinylaniline at −78°C. Controlled experiments without the addition of ketenes revealed that no reaction of *N*-sulfinylaniline occurred in the presence of 10 mol% or 1 equivalent of **4a′** at −78°C.[19] Based on these observations and our previously established reactivity of NHCs towards ketenes, we propose that the catalytic cycle is initiated by the addition of the NHC to the ketene to give enolate **B**, which reacts with *N*-sulfinylanilines **2** to afford adduct **C** (Scheme 3). Ring closure of adduct **C** gives the final product **3** and regenerates the catalyst.

In summary, the enantioselective N-heterocyclic carbene catalyzed [2+2] cycloaddition of ketenes and *N*-sulfinylanilines was developed. Both enantiomers of the cycloadduct of 1,2-thiazetidin-3-one 1-oxides were obtained in very good yields with excellent enantioselectivities using only 1 mol% of the

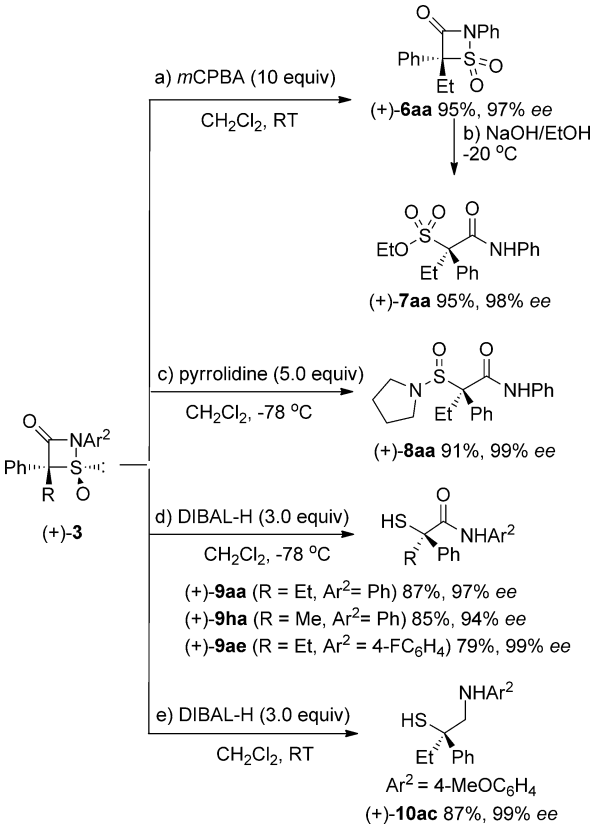
Table 2: Enantioselective [2+2] cycloaddition of ketenes and *N*-sulfinylanilines by NHC **4a′** or **5′**.



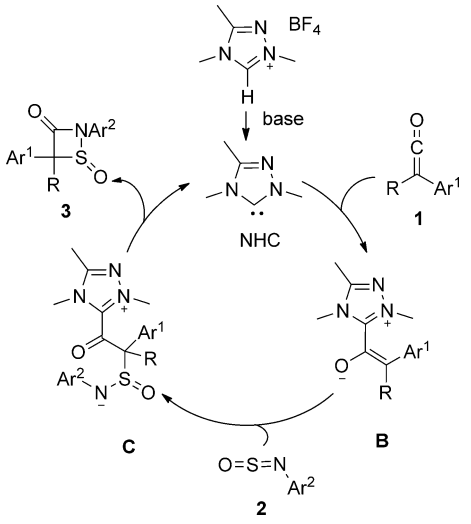
1 **2** (+)-**3** (−)-**3**

Entry	**1** (Ar^1, R)	**2** (Ar^2)	Reaction using **4a′**[a] (+)-**3**	Yield [%][b]	*ee* [%][c]	Reaction using **5′**[a] (−)-**3**	Yield [%][b]	*ee* [%][c]
1	**1a** (Ph, Et)	**2a** (Ph)	(+)-**3aa**	95	99	(−)-**3aa**	94	99
2	**1b** (4-MeC_6H_4, Et)	**2a**	(+)-**3ba**	88	95	(−)-**3ba**	91	93
3	**1c** (4-$MeOC_6H_4$, Et)	**2a**	(+)-**3ca**	93	98	(−)-**3ca**	91	98
4	**1d** (4-BrC_6H_4, Et)	**2a**	(+)-**3da**	93	94	(−)-**3da**	93	94
5	**1e** (4-ClC_6H_4, Et)	**2a**	(+)-**3ea**	89	99	(−)-**3ea**	87	97
6	**1f** (3-ClC_6H_4, Et)	**2a**	(+)-**3fa**	81	81	(−)-**3fa**	87	92
7	**1g** (2-ClC_6H_4, Et)	**2a**	(+)-**3ga**	81[d]	93[d]	(−)-**3ga**	73	88
8	**1h** (Ph, Me)	**2a**	(+)-**3ha**	91	98	(−)-**3ha**	93	98
9	**1i** (Ph, *n*-Pr)	**2a**	(+)-**3ia**	93	97	(−)-**3ia**	95	94
10	**1j** (Ph, *n*Bu)	**2a**	(+)-**3ja**	94	97	(−)-**3ja**	96	96
11	**1k** (Ph, *i*Bu)	**2a**	(+)-**3ka**	86	80	(−)-**3ka**	81	88
12	**1l** (Ph, Ph)	**2a**	**3la**	13	3	(−)-**3la**	81	82
13	**1m** (-$(CH_2)_6$-)	**2a**	**3ma**	91	3	(−)-**3ma**	93	16
14	**1a** (Ph, Et)	**2b** (4-MeC_6H_4)	(+)-**3ab**	81	98	(−)-**3ab**	83	91
15	**1a**	**2c** (4-$MeOC_6H_4$)	(+)-**3ac**	90	99	(−)-**3ac**	87	99
16	**1a**	**2d** (4-ClC_6H_4)	(+)-**3ad**	89	99	(−)-**3ad**	86	99
17	**1a**	**2e** (4-FC_6H_4)	(+)-**3ae**	88	99	(−)-**3ae**	91	99
18	**1a**	**2f** (2-$MeOC_6H_4$)	(+)-**3af**	79	98	(−)-**3af**	87	99
19	**1a**	**2g** (2-ClC_6H_4)	(+)-**3ag**	81	91	(−)-**3ag**	83	95
20	**1a**	**2h** (2-FC_6H_4)	(+)-**3ah**	84	97	(−)-**3ah**	87	98

[a] The NHCs **4a′** and **5′** were freshly generated from the precatalysts **4a** and **5** (1 mol%), respectively, in the presence of Cs_2CO_3 (2 mol%) at room temperature after 30 min, and then used immediately. [b] Yield of the isolated product. [c] Determined by HPLC methods using a chiral stationary phase. [d] Reaction catalyzed by 10 mol% of NHC **4a′**.



Scheme 2. Chemical transformations of thiazetidinone oxide **3**. DIBAL-H = diisobutylaluminum hydride, *m*CPBA = *meta*-chloroperbenzoic acid.



Scheme 3. Proposed catalytic cycle.

NHCs derived from L-pyroglutamic acid or chiral amino indanol. Several enantiopure sulfur-containing organic compounds, including 3-oxo-β-sultams, α-mercapto amides, and β-mercapto amines could be easily prepared from the oxidation or reduction of the resulted 1,2-thiazetidin-3-one 1-oxides.

Experimental Section

Typical procedure: An oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with triazolium salt **4a** (5.7 mg, 0.01 mmol) or **5** (4.0 mg, 0.01 mmol), anhydrous Cs_2CO_3 (7 mg, 0.02 mmol), and 4 Å molecular sieves (50 mg). This tube was closed with a septum, evacuated, and back-filled with argon. Freshly distilled CH_2Cl_2 (5 mL) was added to this mixture, which was then stirred for 30 min at room temperature. The reaction mixture was cooled to −78 °C, and then the ketene **1a** (146 mg, 1.5 mmol) and *N*-sulfinylaniline **2a** (139 mg, 1 mmol) were added. After stirring for 48 h, the reaction mixture was diluted with diethyl ether and passed through a short silica pad. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether 1:100) to give the desired product.

Received: April 11, 2011
Revised: June 20, 2011
Published online: August 25, 2011

Keywords: asymmetric catalysis · cycloaddition · ketenes · N-heterocyclic carbene · sultams

[1] a) W.-Y. Tsang, N. Ahmed, K. Heming, M. I. Page, *Org. Biomol. Chem.* **2007**, *5*, 3993; b) W. Y. Tsang, N. Ahmed, K. Hemming, M. I. Page, *J. Org. Chem.* **2008**, *73*, 4504; c) J. Mulchande, R. C. Guedes, W.-Y. Tsang, M. I. Page, R. Moreira, J. Iley, *J. Med. Chem.* **2008**, *51*, 1783; d) W. Y. Tsang, N. Ahmed, L. P. Harding, K. Hemming, A. P. Laws, M. I. Page, *J. Am. Chem. Soc.* **2005**, *127*, 8946; e) M. Zajac, R. Peters, *Org. Lett.* **2007**, *9*, 2007.

[2] For the synthesis of 1,2-thiazetidin-3-one 1-oxides, see: a) H. Beecken, F. Korte, *Tetrahedron* **1962**, *18*, 1527; b) U. Jäger, M. Scheab, W. Sundermeyer, *Chem. Ber.* **1986**, *119*, 1127; c) T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, N. Kasai, *J. Org. Chem.* **1972**, *37*, 3810; d) A. Dondoni, P. Giorgianni, A. Battaglia, *J. Chem. Soc. Chem. Commun.* **1981**, 350.

[3] a) D. H. Scharf, N. Remme, T. Heinekamp, P. Hortschansky, A. A. Brakhage, C. Hertweck, *J. Am. Chem. Soc.* **2010**, *132*, 10136; b) A. Spannhoff, R. Machmur, R. Heinke, P. Trojer, I. Bauer, G. Brosch, R. Schüle, W. Hanefeld, W. Sippl, M. Jung, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4150; c) C. Anne, S. Turcaud, A. G. S. Blommaert, F. Darchen, E. A. Johnson, B. P. Roques, *ChemBioChem* **2005**, *6*, 1375; d) C. Anne, S. Turcaud, J. Quancard, F. Teffo, H. Meudal, M.-C. Fournié-Zaluski, B. P. Roques, *J. Med. Chem.* **2003**, *46*, 4648.

[4] a) H. Pellissier, *Chiral Sulfur Ligands: Asymmetric Catalysis*, Royal Society of Chemistry, Cambridge, **2009**.

[5] For recent reviews on NHC catalysis, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; c) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77.

[6] For the reviews on asymmetric reactions of ketenes, see: a) T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 6973; *Angew. Chem. Int. Ed.* **2005**, *44*, 6812; b) R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545; c) D. H. Paull, A. Weatherwax, T. Lectka, *Tetrahedron* **2009**, *65*, 6771; d) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542.

[7] L. He, H. Lv, Y.-R. Zhang, S. Ye, *J. Org. Chem.* **2008**, *73*, 8101.

[8] a) X.-N. Wang, P.-L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029; b) X.-N. Wang, Y.-Y. Zhang, S. Ye, *Adv. Synth. Catal.* **2010**, *352*, 1892.

[9] a) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277; b) Smith et al. have also independently reported an NHC-catalyzed reaction of ketenes with imines: N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108.

[10] P.-L. Shao, X.-Y. Chen, S. Ye, *Angew. Chem.* **2010**, *122*, 8590; *Angew. Chem. Int. Ed.* **2010**, *49*, 8412.
[11] a) Y.-R. Zhang, H. Lv, D. Zhou, S. Ye, *Chem. Eur. J.* **2008**, *14*, 8473; b) T.-Y. Jian, P.-L. Shao, S. Ye, *Chem. Commun.* **2011**, *47*, 2381.
[12] a) D. Enders, O Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1351; *Angew. Chem. Int. Ed.* **2006**, *45*, 1327; b) D. Enders, J. Han, *Tetrahedron: Asymmetry* **2008**, *19*, 1367.
[13] a) M. S. Kerr, J. Alaniz, J. R. deAlaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725; b) M. S. Kerr, J. R. deAlaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298.
[14] CCDC 819904 ((−)-**3ha**) contains the 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.
[15] K. Hirota, Y. Kitade, T. Tomishi, Y. Maki, *J. Chem. Soc. Perkin Trans. 1.* **1988**, 2233.
[16] T. R. Todorva, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 354.
[17] J. J. Eisch, Z.-R. Liu, M. P. Boleslawski, *J. Org. Chem.* **1992**, *57*, 2143.
[18] J. M. Bohen, M. M. Joullié, *J. Org. Chem.* **1973**, *38*, 2652.
[19] *N*-sulfinylaniline (**2a**) was recovered in 85% yield.

