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Chiral N-Heterocyclic Carbene Catalyzed Staudinger Reaction of Ketenes with Imines: Highly Enantioselective Synthesis of *N*-Boc β-Lactams

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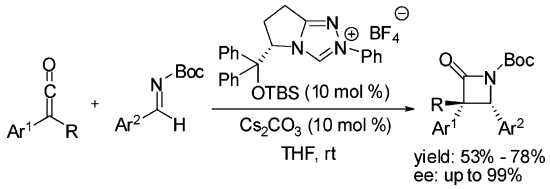
ABSTRACT



N-Heterocyclic carbenes (NHCs) were demonstrated to be efficient catalysts for the Staudinger reaction of ketenes with *N*-tosyl, *N*-benzyloxycarbonyl, or *N-tert*-butoxycarbonyl imines. Chiral NHC 8b, conveniently prepared from L-pyroglutamic acid, catalyzed the reactions of arylalkylketenes with a variety of *N-tert*-butoxycarbonyl arylimines to give the corresponding *cis*-β-lactams in good yields with good diastereoselectivities and excellent enantioselectivities (up to 99% ee). Two possible catalytic pathways, initiated by the addition of NHC to ketenes or imines, were discussed.

The chemistry of N-heterocyclic carbenes (NHCs) has grown dramatically since the discovery of stable carbenes.[1] They have been widely utilized as powerful reagents,[2] applied as ligands for organometallic catalysts,[3] and have developed into nucleophilic organocatalysts.[4] Owing to their capability to attack the carbon−oxygen double bond of aldehydes, NHCs were demonstrated very successfully as catalysts for the umpolung of aldehydes[5] and the extended umpolung of functionalized aldehydes, such as α,β-unsaturated aldehydes,[6] α-haloaldehydes, [7] α,β-epoxyaldehydes,[8] cyclopropanecarboxaldehydes,[9] and β-lactam aldehydes.[10] NHCs were also found to be excellent catalysts for transesterification, acylation, ring-opening polymerization, activation of silylated nucleophiles, and other reactions.[4,11]

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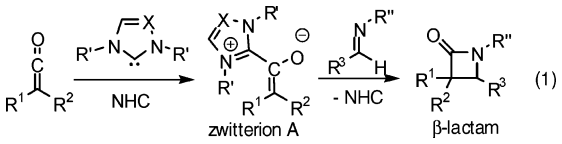
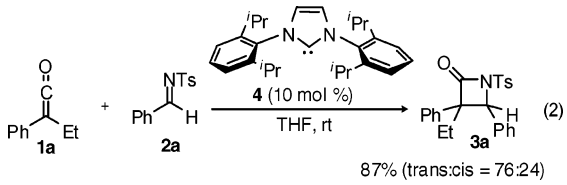
Introduced by Staudinger a century ago, ketenes are remarkable for the diverse range of useful products from their reactions.[12] In line with our research of NHC-catalyzed reactions,[13] we proposed that NHCs may be able to attack ketene to give a reactive zwitterion **A** and thus be potential catalysts for the Staudinger reactions of ketenes with imines to give β-lactams (eq 1).[14,15]



(1)

First reported by Staudinger, the cycloaddition reaction of ketenes with imines is a versatile and efficient route to construct β-lactams.[16] However, there are only a few examples for the catalytic enantioselective Staudinger reactions. Lectka et al. reported their pioneering work that the quinine derivatives, as the nucleophilic catalysts, could catalyze the reaction of ketenes with *N*-tosyl α-iminoesters with high enantioselectivities.[17] This strategy was advanced by Fu et al. to the reaction of ketenes with *N*-tosyl and *N*-triflyl imines to give *cis*- and *trans*-β-lactams, respectively, using planar-chiral derivatives of 4-(dimethylamino)pyridine as catalysts.[18] In this communication, NHCs proved to be efficient catalysts for the Staudinger reaction of ketenes with not only *N*-tosyl but also *N*-*tert*-butoxycarbonyl (Boc) imines.

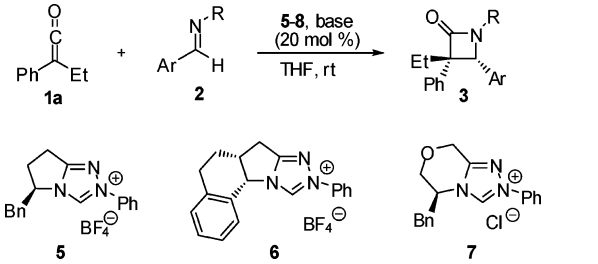
Initially, *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**4**),[19] a stable NHC, was tested for the Staudinger reaction. We were pleased to find that 10 mol % of NHC **4** could catalyze the reaction of phenylethylketene (**1a**) with *N*-tosylphenylimine (**2a**) to give the corresponding β-lactam **3a** in high yield, while only a trace amount of **3a** was detected in the absence of the catalyst (eq 2).



(2)

This result prompted us to explore chiral NHCs for the enantioselective Staudinger reaction (Table 1). Several reported chiral NHC precursors **5**−**7**[20] were found to be efficient catalysts for the reaction of ketene **1a** and *N*-tosyl 2-furylimine (**2b**), but low to moderate enantioselectivities were observed (entries 1−4). Triazolium salts **8a** and **8b**, with bulky diphenyl(trialkylsilyloxy)methyl substituent, were then designed and conveniently synthesized from L-pyroglutamic acid (Scheme 1). Both **8a** and **8b** catalyzed the

Table 1. Investigation of Chiral NHCs for the Staudinger Reaction



entry	**2**: Ar, R	NHC[a]	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	**2b**: 2-furyl, Ts	**5**	93	55:45	−38[e]
2	**2b**: 2-furyl, Ts	**6**	99	62:38	42
3	**2b**: 2-furyl, Ts	**6**	99	78:22	63
4	**2b**: 2-furyl, Ts	**7**	59	55:45	−9[e]
5	**2b**: 2-furyl, Ts	**8a**	99	50:50	58
6	**2b**: 2-furyl, Ts	**8b**	98	67:33	83
7	**2c**: 4-ClC_6H_4, Ts	**8b**	97	36:64	19
8	**2d**: 4-ClC_6H_4, Cbz	**8b**	53	60:40	89
9	**2e**: 4-ClC_6H_4, Boc	**8b**	68	75:25	95
10[f]	**2e**: 4-ClC_6H_4, Boc	**8b**	72	75:25	96

[a] NHCs were generated in situ from the precursors **5**−**8** with 1 equiv base of *t*-BuOK (entries 1 and 2) or Cs_2CO_3 (entries 3−10). [b] Isolated yield. [c] Determined by ^{1}H NMR of the reaction mixture. [d] Enantiomeric excess of the *cis*-isomer. [e] Enantiomers with opposite absolute stereochemistry were obtained. [f] 10 mol % of NHC was used.

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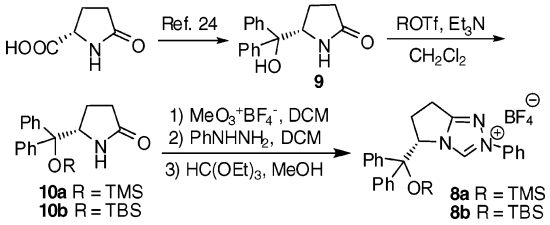
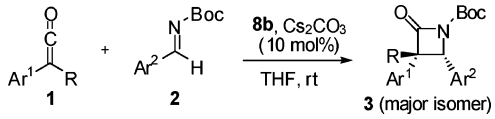
Scheme 1. Synthesis of Chiral NHC Precursors **8a** and **8b**



Staudinger reaction efficiently, while **8b** showed better diastereo- and enantioselectivity (entries 5 and 6). It is surprising to find that the enantioselectivity decreased sharply when *N*-tosyl(4-chlorophenyl)imine **2c** was employed instead of furylimine **2b** (entry 6 vs 7). We conjectured that the electron-deficient 4-chlorophenyl group is the possible reason for the decrease of selectivity. Thus, imines with a less electron-withdrawing protective group were investigated. It was found that the reaction with *N*-benzyloxycarbonyl (Cbz) imine **2d**, and *N*-*tert*-butoxycarbonyl (Boc) imine **2e** afforded the corresponding β-lactams with good *cis*-selectivity and with 89 and 95% ee, respectively (entries 8 and 9). Further experiments showed that decreasing the loading of catalyst **8b** from 20 to 10 mol % made no notable change in yield and selectivity (entry 10).

Substrate scope investigation revealed that a wide variety of ketenes and imines reacted smoothly to afford corresponding β-lactams in good yields with good to high diastereoselectivities and excellent enantioselectivities (Table 2). The *ortho*-substituted arylimines (2-Cl, 2-BrC_6H_4) worked well and benefited the diastereoselectivities (entries 2 and 3). The *meta*- or *para*-substituted arylimines afforded β-lactams with somewhat decreased diastereoselectivities as compared to *ortho*-substituted ones, but excellent enantioselectivities were still achieved (entries 2−5). Arylimines from a strong electron-deficient one (4-$NO_2C_6H_4$) to a less electron-deficient one (2-furyl) worked well (entries 6−8). Arylalkylketenes with either an electron-donating substituent (4-MeO) or an electron-withdrawing substituent (4-Cl) are suitable substrates (entries 9−13). It should be noted that the reaction with alkylimines was sluggish and failed to give the β-lactams under current standard reaction conditions.

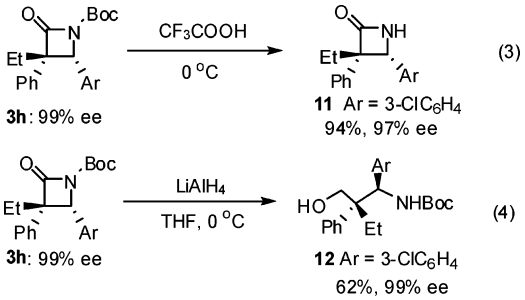
Table 2. Asymmetric Staudinger Reaction Catalyzed by **8b**



entry	**1**: Ar^1, R	**2**: Ar^2	yield (%)[a]	cis/trans[b]	ee (%)[c]
1	Ph, Et	4-ClC_6H_4	**3e**,[d] 72	75:25	96
2	Ph, Et	2-ClC_6H_4	**3f**,[d] 71	91:9	99
3	Ph, Et	2-BrC_6H_4	**3g**, 58	94:6	97
4	Ph, Et	3-ClC_6H_4	**3h**, 66	80:20	99
5	Ph, Et	4-BrC_6H_4	**3i**, 71	78:22	99
6	Ph, Et	4-$NO_2C_6H_4$	**3j**, 75	71:29	99
7	Ph, Et	Ph	**3k**, 64	75:25	99
8	Ph, Et	2-furyl	**3l**, 57	83:17	98
9	Ph, Me	2,4-$Cl_2C_6H_3$	**3m**, 53	86:14	93
10	4-$MeOC_6H_4$, Et	2-ClC_6H_4	**3n**, 78	93:7	91
11	4-$MeOC_6H_4$, Et	2,4-$Cl_2C_6H_3$	**3o**, 62	89:11	96
12	4-ClC_6H_4, Et	2-ClC_6H_4	**3p**, 61	99:1	97
13	4-ClC_6H_4, Et	4-ClC_6H_4	**3q**, 53	83:17	99

[a] Isolated yield. [b] Determined by ^{1}H NMR of the reaction mixture. [c] Enantiomeric excesses of the *cis*-isomer and the *trans*-isomer of **3e**, **3h**, **3j**, **3k**, **3n**, and **3o** are 27, 65, 81, 67, 10, and 30%, respectively. [d] The absolute configuration of **3f** and **3e** was determined by X-ray and CD spectra, respectively.

An advantage of this work is that the resulting *N*-Boc-protected β-lactam **3** could be easily deprotected to afford the free β-lactam in high yield (eq 3). Furthermore, the β-lactam ring was reductively opened by $LiAlH_4$ to afford γ-amino-alcohol without erosion in stereochemical purity (eq 4).



Similarly to the mechanisms suggested by Fu et al. in their catalytic Staudinger reactions,[18a] the NHC may add to ketene (mechanism A) or imine (mechanism B) to initiate the catalytic cycle (Figure 1).

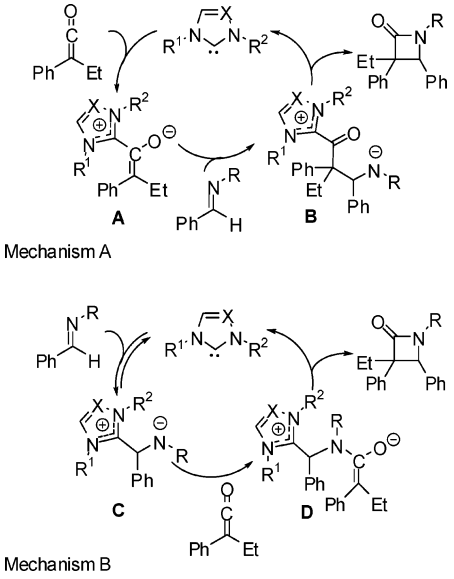
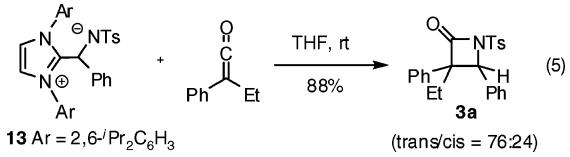


Figure 1. Two possible catalytic mechanisms.

Experiments showed NHC **8b′** (generated from precursor **8b** in situ) could react with ketene **1a** rapidly, but we failed to identify the ketene−NHC zwitterion **A**.

It was reported that NHCs could react with *N*-tosyl imines,[21] and we successfully isolated the NHC−imine adduct **13** (intermediate **C** in Figure 1) from the reaction of NHC **4** with *N*-tosyl imine **2a**.[13,22] It was found that adduct **13** could react with phenylethylketene to give β-lactam **3a** in 88% yield with the same diastereoselectivity as that in the catalytic version (eq 2 vs eq 5). However, it should be noted that the formation of adduct **13** is reversible,[13] and the cyclization of intermediate **D** to β-lactam is disfavored according to Baldwin's rules.[23] Thus, it cannot be ruled out that adduct **13** may decompose in situ to imine and NHC and then form β-lactam **3a** by mechanism A.



As for the reaction of ketenes with less electron-deficient imines, such as *N*-Cbz and *N*-Boc imines, mechanism A is apparently favored over mechanism B because the NHC reacts very sluggishly with those imines.

In conclusion, chiral NHCs were proven for the first time to be efficient catalysts for the Staudinger reaction of ketenes with imines. The concept of activation of ketenes by NHC may find further application in the catalytic transformation of ketenes, especially those of the cycloaddition reaction. Furthermore, to the best of our knowledge, this communication represents the first example of catalytic enantioselective Staudinger reaction with *N*-Boc imines. Several advantages of this methodology, including ready availability of catalyst **8b**, excellent enantioselectivities, facile removal of the Boc group, and easy scale-up of the reaction,[25] make it potentially useful in the synthesis of *cis*-β-lactams with α-quaternary and β-tertiary stereocenters. Further investigation of substrate scope and the detailed reaction mechanism is underway in our laboratory.

Acknowledgment. We are grateful for the financial support from Chinese Academy of Sciences and Natural Sciences Foundation of China (No. 20602036).

Supporting Information Available: Experimental procedures and compound characterization including synthesis of NHC precursors **8a** and **8b**, crystal structure data of lactam **3f**, and CD spectra of lactams **3e** and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Scaling up the reaction from 0.51 mmol (imine **2h**) to 8.6 mmol made no notable difference in yield and selectivity.