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Enantioselective Synthesis of Aza-β-lactams via NHC-Catalyzed [2 + 2] Cycloaddition of Ketenes with Diazenedicarboxylates

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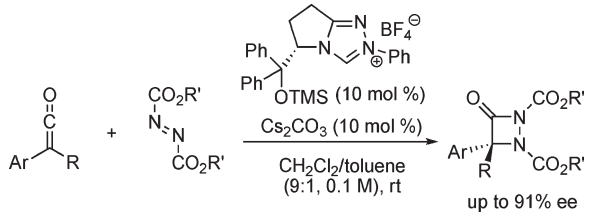
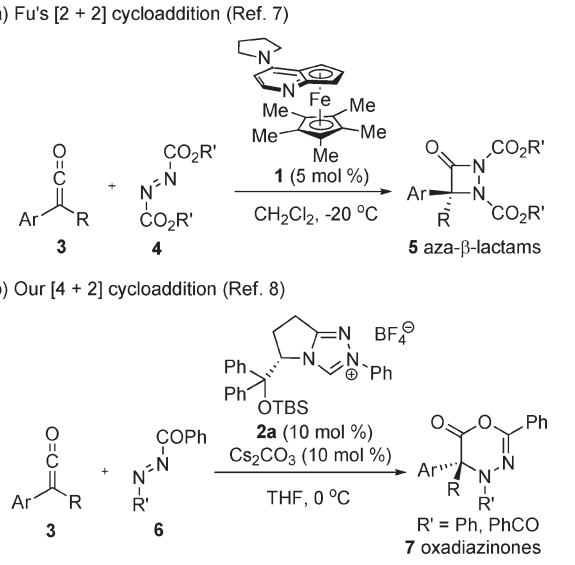


N-Heterocyclic carbenes were found to be efficient catalysts for the formal [2 + 2] cycloaddition of aryl(alkyl)ketenes and diazenedicarboxylates to give the corresponding aza-β-lactams in good yields with up to 91% ee. The *N*-substituent (carboxylate vs benzoyl) of diazenes played an important role to control the reaction modes (formal [2 + 2] vs [4 + 2] cycloaddtions).

As the aza analogues of β-lactams, aza-β-lactams show some interesting biological activities[1] and are useful intermediates for the synthesis of α-amino acids and heterocyclic compounds.[2] In 1925, Ingold and Weaver reported the first [2 + 2] cycloaddition of ketenes and diazenes to give aza-β-lactams.[3−5] Lately, Taylor and co-workers were the main contributors for the synthesis and application of aza-β-lactams.[6] Recently, Berlin and Fu reported the first enantioselective [2 + 2] cycloaddition of ketenes with diazenedicarboxylates catalyzed by their planar-chiral 4-pyrrolidinopyridine derivatives (Scheme 1a).[7] Interestingly, we found that the reaction of ketenes and *N*-benzoyldiazenes catalyzed by chiral *N*-heterocyclic carbenes (NHCs) gave predominately the formal [4 + 2] cycloaddition of ketenes in high yield with good enantioselectivities (Scheme 1b).[8]

SCHEME 1. [2 + 2] and [4 + 2] Cycloadditions Reported



The two reaction modes ([4 + 2] and [2 + 2]) prompt us to think whether the catalysts or the different substituents of diazenes control the reaction modes. To answer this question, two more experiments were carried out. It was found that NHC **2a′**, generated freshly from the precursor **2a** and Cs_2CO_3, could catalyze the reaction of phenyl(ethyl)ketene (**3a**) and diethyl diazenedicarboxylate (**4a**) to give [2 + 2] cycloaddition product in 38% yield with 87% ee, and no [4 + 2] cycloaddition product was detected (Scheme 2a). The other experiment showed that DMAP-catalyzed reaction of ketene **3a** and *N*-phenyl-*N′*-benzoyldiazene gave the [4 + 2] cycloaddition product (Scheme 2b).

For the reactions catalyzed by NHC, the reaction mode is changed from [4 + 2] to [2 + 2] when the diazene is changed from *N*-benzoyldiazene to diazenedicarboxylate (Scheme 1b vs

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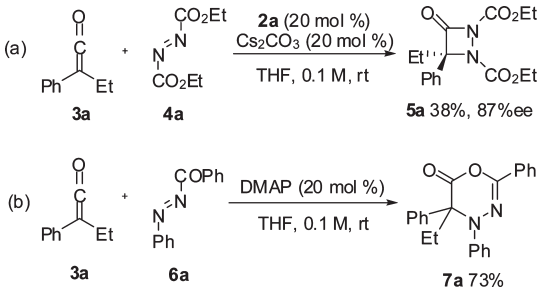
SCHEME 2. Control Experiments



Scheme 2a). For the reaction catalyzed by pyridine derivatives,[9] change of the diazenes also led to the change of reaction modes (Scheme 1a vs Scheme 2b). In other words, the reaction of ketenes and diazenedicarboxylates, catalyzed by either pyridine derivative (Scheme 1a) or NHC (Scheme 2a) gave the [2 + 2] cycloaddition product, whereas the reaction of ketenes and *N*-benzoyldiazenes, catalyzed by either NHC (Scheme 1b) or DMAP (Scheme 2b), gave the [4 + 2] cycloaddition product. Thus, we conclude that the different reaction modes are predominantly controlled by the different substituents of the diazenes.[10] The different behaviors of carbonyl groups of benzoyl and carboxylate may contribute to the two different reaction modes.

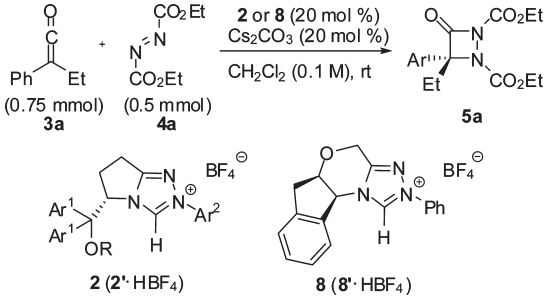
Encouraged by these results, we decided to investigate the NHC-catalyzed [2 + 2] cycloaddition of ketenes with diazenedicarboxylates to synthesize optically active aza-β-lactams. A series of NHCs were then tested for reactions (Table 1). Interestingly, when the reaction was carried out in dichoromethane (the solvent of choice in Fu's work), the yield was increased to 88% with 85% ee (Table 1, entry 1 vs Scheme 2a). Unexpectedly, the reaction catalyzed by less sterically hindered NHC **2b′** with a TMS protective group gave the aza-β-lactams in very good yield with slightly better enantioselevtivity than with NHC **2a′** (entry 2 vs entry 1). Installing an electron-donationg group gives NHC **2c′** (Ar^2 = *p*-methoxylphenyl), which showed similar result as with NHC **2a′** (entry 3). The reaction catalyzed by NHC **2d′** (Ar^2 = mesityl) led to low yield and enantioselectivity (entry 4).

A series of *N*-heterocyclic carbenes (**2e′**−**h′**) with a free hydroxyl group were then tested.[11] NHC **2e′** did catalyze this cycloaddition, but with little asymmetric induction (Table1, entry 5). Both NHC **2f′** and **2g′** catalyzed the reaction with improved results (entries 6 and 7). The enantioselectivity could be switched when NHC **2h′** was employed, but low yield resulted (entries 8 and 9).[8] The reaction catalyzed by Rovis' catalyst **8′**[12] also afforded the desired product in 48% yield with 88% ee (entry 10).

Further solvent screening revealed that reaction in dichloromethane was better than in acetonitrile, THF, and toluene (Table 2, entries 1−6). Lowering the temperature had no positive impact on either the yield or the enantioselectivity (entry 7). When the reaction was run in dichloromethane with other co-solvents, the high yields were retained and slightly better enantioselectivities were achieved (entries 8−10). Slow addition of the solution of ketene **3a** by a syringe pump showed some benefits for the enantioselectivity (entry 11 vs 12). Reactions with 10 or 5 mol % NHC loading also gave the desired product in good yields with good enantioselectivities (entries 11 and 12).

A variety of ketenes with different steric and electronic properties were then examined (Table 3). Ketenes bearing an electron-donating group (4-Me or 4-MeO) on the phenyl ring gave the desired aza-β-lactacm in a slightly decreased yield with moderate to good enantiomeric excess (entries 2 and 3). When an electron-withdrawing group (Cl or Br) was introduced at the *para* or *meta* position on the phenyl ring, the

TABLE 1. Chiral NHCs Screening[a]



entry	**2** (Ar^1, Ar^2, R) or **8**	yield (%)[b]	ee (%)[c]
1	**2a**: Ph, Ph, TBS	88	85
2	**2b**: Ph, Ph, TMS	94	88
3	**2c**: Ph, PMP, TBS	88	84
4	**2d**: Ph, Mes, TMS	53	68
5	**2e**: Ph, Ph, H	43	8
6	**2f**: 3,5-$(CF_3)_2C_6H_3$, Ph, H	69	59
7	**2g**: 3,5-$(CF_3)_2C_6H_3$, PMP, H	71	58
8	**2h**: Ph, Mes, H	26	−70[d]
9[e]	**2h**: Ph, Mes, H	26	−87[d]
10	**8**	48	−88[d]

[a]NHCs **2′** and **8′** were generated from the NHC precursor **2** and **8** with Cs_2CO_3 in THF at room temperature in 10 min and used immediately. [b]Isolated yields. [c]Deterimined by chiral HPLC. [d]*ent*-**5a** was obtained as the major enantiomer. [e]Toluene was used as the solvent.

TABLE 2. Optimization of Conditions for the Formal [2 + 2] Cycloaddition of 3a and 4a catalyzed by NHC 2b′[a]

entry	conditions	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2, rt	94	88
2	CH_3CN, rt	78	83
3	THF, rt	81	86
4	toluene, rt	81	85
5	$CHCl_3$, rt	88	84
6	$ClCH_2CH_2Cl$, rt	79	85
7	CH_2Cl_2, 0 °C	69	87
8	CH_2Cl_2/THF (9:1), rt	91	90
9	CH_2Cl_2/ether (9:1), rt	91	89
10	CH_2Cl_2/toluene (9:1), rt	90	90
11[d]	CH_2Cl_2/toluene (9:1), rt	93	89
12[d,e]	CH_2Cl_2/toluene (9:1), rt	93	91
13[e,f]	CH_2Cl_2/toluene (9:1), rt	87	89

[a]Ketene **3a** (0.75 mmol), diazene **4a** (0.5 mmol), NHC precursor **2b** (0.1 mmol), and Cs_2CO_3 (0.1 mmol) were employed. [b]Isolated yields. [c]Deterimined by chiral HPLC. [d]NHC precursor **2b** (0.05 mmol) and Cs_2CO_3 (0.05 mmol) were used. [e]Ketene **3a** was added by syringe pump over 1 h. [f]NHC precursor **2b** (0.025 mmol) and Cs_2CO_3 (0. 025 mmol) were used.

(9) DMAP (*N*,*N*-dimethylpyridin-4-amine) was used as the simplified achiral catalyst of pyridine derivative **1**, for its read availability.

(10) Reaction conditions such as solvents also showed some influence on the formation of [2 + 2] or [4 + 2] cycloaddition product. See ref 8 and its Supporting Information for detail.

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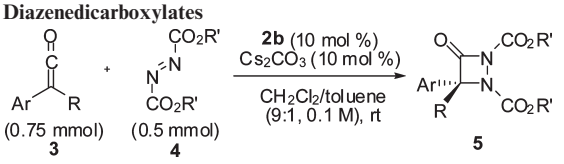
TABLE 3. Enantioselective Formal [2 + 2] Cycloaddition of Ketenes with Diazenedicarboxylates



entry	3 (Ar, R)	4 (R′)	5	yield (%)[a]	ee (%)[b]
1	**a**: Ph, Et	**a**: Et	**aa**	93	91
2	**b**: 4-MeC_6H_4, Et	**a**: Et	**ba**	74	81
3	**c**: 4-$MeOC_6H_4$, Et	**a**: Et	**ca**	95	65
4	**d**: 4-ClC_6H_4, Et	**a**: Et	**da**	90	90
5	**e**: 4-BrC_6H_4, Et	**a**: Et	**ea**	93	91
6	**f**: 3-ClC_6H_4, Et	**a**: Et	**fa**	90	90
7	**g**: 2-ClC_6H_4, Et	**a**: Et	*ent*-**ga**	52	−57[c]
8	**h**: Ph, Me	**a**: Et	**ha**	65	79
9	**i**: Ph, *n*-Pr	**a**: Et	**ia**	84	91
10	**j**: Ph, *n*-Bu	**a**: Et	**ja**	83	89
11	**k**: 4-ClC_6H_4, *n*-Bu	**a**: Et	**ka**	92	90
12	**l**: 4-ClC_6H_4, *i*-Pr	**a**: Et	*ent*-**la**	93	−35[c]
13	**m**: Bn, Et	**a**: Et	**ma**[d]	93	33
14	**a**: Ph, Et	**b**: Me	**ab**	88	85
15	**a**: Ph, Et	**c**: *i*-Pr	**ac**	67	89
16	**a**: Ph, Et	**d**: *t*-Bu	**ad**	91	91

[a]Isolated yields. [b]Deterimined by chiral HPLC. [c]The minus ee value indicates that an opposite enantioselectivity is observed. [d]The absolute stereochemistry of **5ma** was not determined.

corresponding adduct was obtained in excellent yield with very high ee value (entries 4−6). Ethyl(2-chlorophenyl)-ketene worked well under the standard condition and afforded *ent*-**5ga** in 52% yield with 57% ee (entry 7). Ketenes with methyl, *n*-propyl, and *n*-butyl groups afforded the products in good yields with high enantioselectivities (entries 8−11). A ketene with an isopropyl substituent also proved to be a suitable substrate for this reaction and gave the product in 93% yield with opposite enantioselectivity (entry 12). The reaction of dialkylketene **3m** gave the cycloaddition adduct in 93% yield with 33% ee (entry 13).

Several other dialkyl diazenedicarboxylates were then examined. All of the dimethyl, diisoproyl, and di(*tert*-butyl) diazenedicarboxylates worked well for the formal [2 + 2] cycloaddition reaction (Table 3, entries 1, 14−16).

A proposed catalytic cycle for this NHC-catalyzed reaction is depicted in Figure 1. NHC attacks ketene to give triazolium enolate **9**. Nucleophilic addition of the enolate **9** to diazenedicarboxylate generates zwitterionic intermediates **10**, followed by an intramolecular cyclization to give the formal [2 + 2] cycloaddition adducts **5** and regenerate the catalyst.

In summary, highly enantioselective synthesis of aza-β-lactams was realized by the *N*-heterocyclic carebenes-catalyzed formal [2 + 2] cycloaddition of alkylarylketenes and diazenedicarboxylates. The *N*-substituent (carboxylate vs benzoyl) of the diazenes plays an important role to control the reaction modes (formal [2 + 2] vs [4 + 2] cycloaddtions).

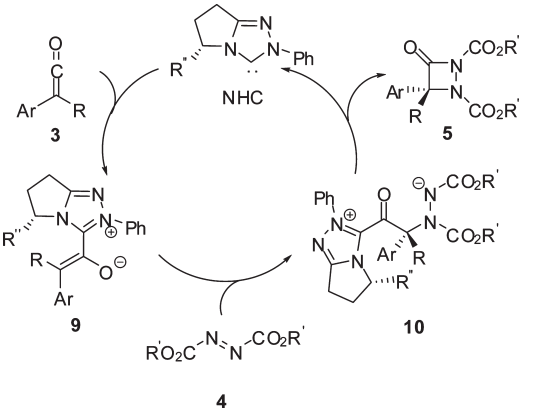


FIGURE 1. Proposed catalytic cycle.

Experimental Section

General Procedure for the [2 + 2] Cycloaddtion of Ketenes with Diazenedicarboxylates Catalyzed by NHC. To a solution of NHC **2b′**, which was generated freshly from the NHC precursor **2b** (26.4 mg, 0.05 mmol) and Cs_2CO_3 (16.3 mg, 0.05 mmol) in dichloromethane/toluene (v/v, 9:1, 3 mL) at room temperature for 10 min, was added diazenedicarboxylate **4a** (87.1 mg, 0.5 mmol). A solution of phenyl(ethyl)ketene **3a** (109.6 mg, 0.75 mmol) in dichloromethane/toluene (v/v, 9:1, 2 mL) was added by a syringe pump over 1 h. After stirring for another 1 h at room temperature, the reaction mixture was diluted with diethyl ether and passed through a short silica gel pad. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel to give the desired product (**5aa**). Yield: 148 mg (93%); R_f = 0.23 (petroleum ether/diethyl ether, 5:1); colorless oil; $[\alpha]^{25}_D$ −19.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.34−7.25 (m, 3H), 4.30−4.23 (m, 2H), 2.35−2.30 (m, 1H), 2.23−2.18 (m, 1H), 1.30−1.25 (m, 3H), 1.13 (t, J = 7.0 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 157.4, 147.8, 134.9, 128.8, 128.5, 126.0, 90.3, 64.0, 63.2, 28.4, 14.1, 14.0, 8.4. HPLC analysis: 91% ee [Daicel CHIRALPAK OD-H column; 20 °C, 254 nm, 1.0 mL/min; solvent system, 2-propanol/hexane = 5:95; t_R = 10.1 min (minor), 14.0 min (major)].

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.