Asymmetric Catalysis

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[4+2] Cycloaddition of Ketenes with *N*-Benzoyldiazenes Catalyzed by N-Heterocyclic Carbenes**

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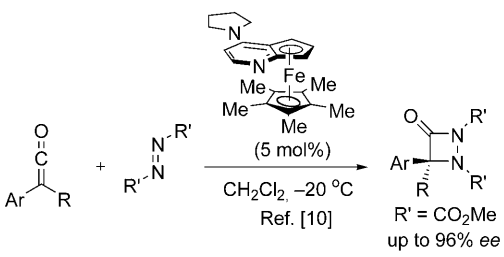
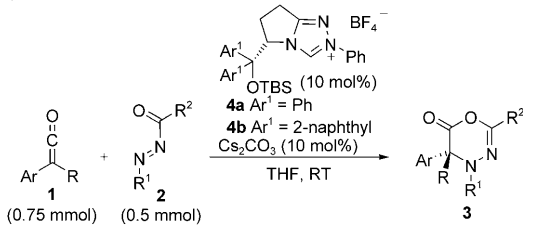
The cycloaddition reactions of ketenes are useful approaches to heterocyclic compounds.[1] Recently, N-heterocyclic carbenes (NHCs)[2] were found to be efficient catalysts for the [2+2] ketene/imine,[3] ketene/aldehyde,[4] and [4+2] ketene/enone[5] cycloaddition reactions. Herein we report an unprecedented enantioselective [4+2] cycloaddition reaction of ketenes with *N*-benzoyldiazenes catalyzed by chiral NHCs to give 1,3,4-oxadiazin-6-ones.[6] In addition to its potential biological activity,[7] this heterocycle is highly functionalized and is a useful intermediate in organic synthesis.[8] For an example, it can be regarded as the masked α,α-disubstituted amino acid derivative.[9] Interestingly, Berlin and Fu reported a [2+2] cycloaddition of ketenes with *N*,*N*′-dimethoxycarbonyldiazenes catalyzed by their planar-chiral 4-pyrrolidinopyridine derivatives [Eq. (1)].[10,11] The different mode of reaction ([4+2] versus [2+2] cycloaddition) prompted us to report our results herein.[12]



(1)

After the initial investigation and the optimization of the reaction conditions,[13] we found that in the presence of 10 mol% of NHC **4a′** or **4b′**, generated from the corresponding NHC precursor **4a** or **4b** with Cs_2CO_3,[14] a variety of ketenes and *N*-aryl-*N*′-benzoyldiazenes **2** could react to give the corresponding [4+2] cycloaddition products in good yields with good enantioselectivities (Table 1). Alkylarylketenes with both electron-donating (**1b** and **1c**) and electron-withdrawing groups (**1d** and **1e**) worked well (Table 1, entries 1–6). However, neither (2-chlorophenyl)ethylketene (**1f**) nor (1-naphthyl)ethylketene (**1g**) led to product (Table 1, entries 7 and 8). The reaction of benzylethylketene (**1h**) gave the cycloaddition product in good yield but with very little enantioselectivity (Table 1, entry 9), and high enantioselectivities were obtained for the reaction of phenylmethylketene (**1i**) and phenylpropylketene (**1j**; Table 1, entries 10 and 11). Both electron-donating and electron-withdrawing groups on the diazene are tolerated (Table 1, entries 12–14). Interestingly, precatalyst **4a** is better than **4b** in some cases (Table 1, entry 2 versus 3).

Table 1: Cycloaddition of ketenes with *N*-aryl-*N*′-benzoyldiazenes catalyzed by NHC.[a,b]



Entry	**1** (Ar, R)	**2** (R^1, R^2)	**3**	Yield [%][c]	*ee* [%][d]
1	**1a** (Ph, Et)	**2a** (Ph, Ph)	**3aa**	93	94
2[b]	**1b** (4-MeC_6H_4, Et)	**2a** (Ph, Ph)	**3ba**	79	90
3	**1b** (4-MeC_6H_4, Et)	**2a** (Ph, Ph)	**3ba**	64	79
4	**1c** (4-$MeOC_6H_4$, Et)	**2a** (Ph, Ph)	**3ca**	88	93
5	**1d** (4-ClC_6H_4, Et)	**2a** (Ph, Ph)	**3da**	92	91[e]
6	**1e** (4-BrC_6H_4, Et)	**2a** (Ph, Ph)	**3ea**	90	90
7[b]	**1f** (2-ClC_6H_4, Et)	**2a** (Ph, Ph)	**3fa**	0	–
8	**1g** (1-naphthyl, Et)	**2a** (Ph, Ph)	**3ga**	0	–
9	**1h** ($PhCH_2$, Et)	**2a** (Ph, Ph)	**3ha**	75	8
10	**1i** (Ph, Me)	**2a** (Ph, Ph)	**3ia**	85	89
11[b]	**1j** (Ph, *n*Pr)	**2a** (Ph, Ph)	**3ja**	69	90
12	**1a** (Ph, Et)	**2b** (Ph, 4-ClC_6H_4)	**3ab**	92	94
13	**1a** (Ph, Et)	**2c** (Ph, 4-MeC_6H_4)	**3ac**	82	84
14	**1a** (Ph, Et)	**2d** (4-$MeOC_6H_4$, Ph)	**3ad**	57	83

[a] The NHCs **4′** were freshly generated from precatalysts **4** with Cs_2CO_3 in THF (2 mL) at RT for 10 min, followed by the addition of diazene and slow addition of the ketene by using a syringe pump over a 1 h period. [b] Precatalyst **4a** used for entries 2, 7, and 11, and **4b** for other entries. [c] Yields of isolated products. [d] Determined by chiral HPLC analysis. [e] The absolute configuration was determined by X-ray crystallography. TBS = *tert*-butyldimethylsilyl.

To expand the scope of the diazenes for this reaction, *N*,*N*′-dibenzoyldiazene (**5a**) was investigated. After the optimization of the reaction conditions,[13] it was found that a wide variety of alkylarylketenes worked well for the reaction with *N*,*N*′-dibenzoyldiazene (**5a**; Table 2). Both electron-rich and electron-deficient alkylarylketenes afforded

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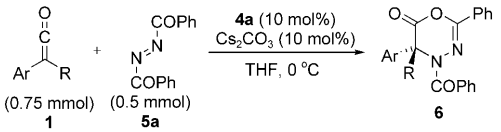
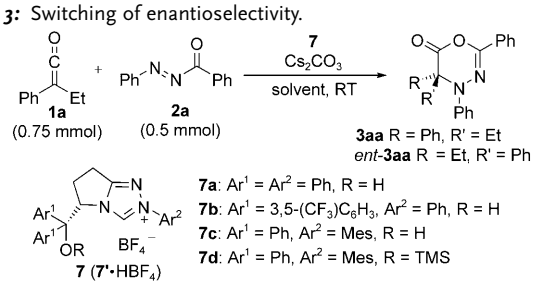
Table 2: Cycloaddition of ketenes with *N*,*N*′-dibenzoyldiazenes catalyzed by NHC.[a]



Entry	**1** (Ar, R)	**6**	Yield [%][b]	*ee* [%][c]
1	**1a** (Ph, Et)	**6aa**	70	97
2	**1b** (4-MeC_6H_4, Et)	**6ba**	55	90
3	**1c** (4-MeOC_6H_4, Et)	**6ca**	62	73
4	**1d** (4-ClC_6H_4, Et)	**6da**	78	95
5	**1e** (4-BrC_6H_4, Et)	**6ea**	74	97
6	**1k** (3-ClC_6H_4, Et	**6ka**	32	72
7	**1f** (2-ClC_6H_4, Et)	*ent*-**6fa**	36	−63[d]
8	**1g** (1-naphthyl, Et)	*ent*-**6ga**	27	−76[d]
9	**1j** (Ph, *n*Pr)	**6ja**	79	96
10	**1l** (4-ClC_6H_4, *n*Bu)	**6la**	85	94
11	**1m** (4-ClC_6H_4, *i*Pr)	*ent*-**6ma**	55	−64[d]
12	**1h** (PhCH_2, Et)	**6ha**	38	3
13[e]	**1a** (Ph, Et)	**6aa**	63	95

[a] See note [a] in Table 1. [b] Yields of isolated products. [c] Determined by HPLC analysis. [d] Opposite enantioselectivity is observed. [e] **1a** (7.5 mmol) and **5a** (5.0 mmol) was employed.

Table 3: Switching of enantioselectivity.



Entry	**7**, mol %,[a] solvent	Yield [%][b]	*ee* [%][c,d]
1	**7a**, 20, THF	40	84
2	**7b**, 20, THF	46	90
3	**7c**, 20, THF	86	−92
4	**7d**, 20, THF	55	−64
5	**7c**, 20, CH_2Cl_2	18	−90
6	**7c**, 20, toluene	79	−96
7	**7c**, 10, toluene	76	−94
8[e]	**7c**, 10, toluene	52	−89
9[e]	**7c**, 10, THF	62	−88

[a] The amount of Cs_2CO_3 used was the equivalent to the mol % of the precatalyst used for each reaction. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] *ent*-**3aa** was obtained as the major enantiomer for entries 3–9. [e] Ketenes were added by using a syringe pump over a 1 h period.

the [4+2] cycloaddition reaction products in good yields with good to high enantioselectivities (Table 2, entries 1–5). The reaction using (3-chlorophenyl)ethylketene (**1k**) resulted in a low yield and decreased enantioselectivity (Table 2, entry 6). Notably, ketenes with bulky substituents (**1f**, **1g**), which did not work for the reaction with *N*-phenyl-*N*′-benzoyldiazene (**2a**), worked in the reaction with *N*,*N*′-dibenzoyldiazene (**5a**) albeit in low yield and with the opposite enantioselectivity (Table 2, entries 7 and 8). Ketenes with *n*-propyl (**1j**) and *n*-butyl (**1l**) groups afforded the products in good yields with highly enantioselectivities (Table 2, entries 9 and 10). However, a ketene having an isopropyl group (**1m**) gave the product in low yield and with the opposite enantioselectivity (Table 2, entry 11). The reaction of benzylethylketene (**1h**) gave the cycloaddition product in low yield with very low enantioselectivity (Table 2, entry 12). Notably, the good yield and high enantioselectivity for the reaction between **1a** and **5a** were maintained when the reaction was scaled up to 5.0 mmol (Table 2, entry 13).

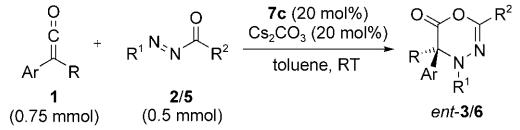
Recently, we found that the silyl group on NHC precursors **4** could be removed and to furnish the NHC precursors **7** with a free hydroxy group.[15] NHC precursors **7a**–**c** were therefore synthesized and tested as precatalysts (Table 3). Oxadiazinone **3aa** was obtained as the major enantiomer with a slightly decreased enantioselectivity when **7a** and **7b** were used (Table 3, entries 1–2). However, it is very interesting that the enanitoselectivity was totally switched and a −92 % *ee* was achieved when NHC precatalyst **7c** (Ar^1 = Ph, Ar^2 = Mes, R = H) was employed (Table 3, entry 3). Additional experiments showed that NHC precatalyst **7d** (Ar^1 = Ph, Ar^2 = Mes, R = TMS) could also switch the enantioselectivity but with a lower *ee* value (Table 3, entry 4). Solvent screening revealed that toluene is a good choice (Table 3, entries 5–6). Reducing the loading of catalyst to 10 mol % led to decreased yield and enantioselectivity (Table 3, entry 7), and the slow addition of the ketene had no positive impact on the reaction (Table 3, entries 8 and 9).

The switch in enantioselectivity to give *ent*-**3** by employing NHC precursor **7c** was also observed for the reaction of several other ketenes and *N*-aryl-*N*′-benzoyldiazenes (Table 4, entries 1–8). However the reaction of ketene and *N*,*N*′-dibenzoyldiazene catalyzed by **7c** gave *ent*-**6aa** in low yield with moderate enantioselectivity (Table 4, entry 9).

The 1,3,4-oxadiazin-6-one **3aa** reacted with methanol to give the ring-opening product α,α-disubstituted α-amino acid derivative **8** in 99 % yield with high enantiopurity [Eq. (2)].

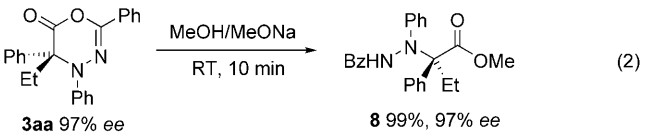
The NHC-catalyzed [4+2] cycloadditions of ketenes with diazenes are possibly initiated by the nucleophilic addition of the NHC to the ketene to give triazolium enolate **9** (Figure 1),

Table 4: Synthesis of *ent*-**3**/**6** catalyzed by NHC **7c**′.



Entry	**1** (Ar, R)	**2**/**5** (R^1, R^2)	*ent*-**3**/**6**	Yield [%][b]	*ee* [%][c]
1	**1a** (Ph, Et)	**2a** (Ph, Ph)	*ent*-**3aa**	79	−96
2	**1b** (4-MeC_6H_4, Et)	**2a** (Ph, Ph)	*ent*-**3ba**	78	−95
3	**1c** (4-MeOC_6H_4, Et)	**2a** (Ph, Ph)	*ent*-**3ca**	85	−95
4	**1e** (4-BrC_6H_4, Et)	**2a** (Ph, Ph)	*ent*-**3ea**	61	−76
5	**1i** (Ph, Me)	**2a** (Ph, Ph)	*ent*-**3ia**	47	−86
6	**1j** (Ph, *n*Pr)	**2a** (Ph, Ph)	*ent*-**3ja**	76	−90
7	**1a** (Ph, Et)	**2b** (Ph, 4-ClC_6H_4)	*ent*-**3ab**	89	−97
8	**1a** (Ph, Et)	**2c** (Ph, 4-MeC_6H_4)	*ent*-**3ac**	76	−88
9	**1a** (Ph, Et)	**5a** (PhCO, Ph)	*ent*-**6aa**	25	−50

[a] Yields of isolated products. [b] Determined by HPLC analysis.



(2)

which reacts with the diazene by an inverse electron demand Diels–Alder reaction to give the [4+2] cycloaddition adduct **10**. Subsequent elimination of the NHC furnishes the corresponding 1,3,4-oxadiazin-6-ones and regenerates the NHC catalyst.[16]

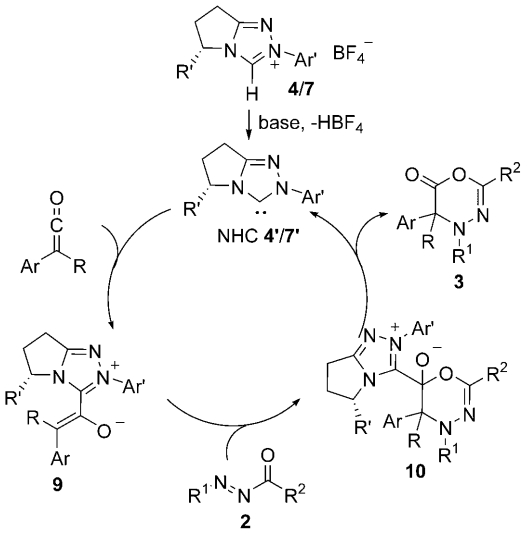


Figure 1. Possible catalytic cycle.

The X-ray crystallographic structures of NHC precursors **4a** and **7c** revealed that the *N*-phenyl group is coplanar with the triazole in NHC precursor **4a**, whereas the *N*-mesityl group is perpendicular to the triazole in NHC precursor **7c**.[17] On the basis of the structural difference between **4a** and **7c** and the enantioselectivites observed, two possible transition states are proposed (Figure 2). In transition state A (TS A), NHC–ketene adduct **9** is in a coplanar conformation in which the *N*-phenyl group of NHC, the triazole, and the enloate are coplanar. In transition state B (TS B), NHC–ketene adduct **9** is in a perpendicular conformation in which both the *N*-mesityl group and the enolate are perpendicular to the triazole. For the reaction of most ketenes catalyzed by NHC **4a′** and **4b′**, coplanar TS A is favored to give cycloaddition products **3** and **6** as the major enantiomer (Tables 1 and 2).

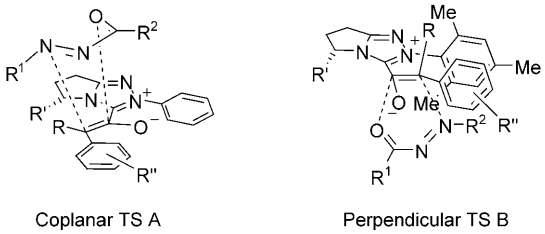


Figure 2. Possible transition states.

For the reactions catalyzed by NHC **7c′**, the perpendicular TS B is favored and gives *ent*-**3** and *ent*-**6** as the major enantiomer (Table 4). For the reactions of ketenes with bulky substituents catalyzed by NHC **4a′**, the coplanar TS A cannot be maintained, so the opposite enantioselectivity is observed (Table 2, entries 7, 8, and 11).

In conclusion, an unprecedented catalytic enantioselective [4+2] cycloaddition of alkylarylketenes with *N*-aryl-*N′*-benzoyldiazenes or *N*,*N′*-dibenzoyldiazenes to give 1,3,4-oxadiazin-6-ones was developed by employing NHC catalysts. The enantioselectivities could be switched for most reactions by adjusting the substitutents in the NHC catalysts. The ready availability of the NHC precatalysts and highly and switchable enantioselectivities of the reaction make it potential useful to synthesize the 1,3,4-oxadiazin-6-one heterocycles.

Experimental Section

General Procedure (Table 1): Trazolium salt **4b** (33.5 mg, 0.05 mmol) and anhydrous Cs_2CO_3 (16.3 mg, 0.05 mmol) was added to an oven-dried 50 mL Schlenk tube equipped with a stir bar. This tube was closed with a septum, evacuated, and back-filled with argon. Freshly distilled THF (2 mL) was added to the reaction mixture and then stirred for 10 min at room temperature. *N*-Benzoyl-*N′*-phenyldiazene (105 mg, 0.5 mmol) was then added, affording a red solution. A solution of phenylethylketene (109.6 mg, 0.75 mmol) in THF (2 mL) was added slowly by using a syringe pump over a period of 1 h (2 mL h^{-1}). After the addition of the ketene, the red color disappeared, and the heterogeneous mixture was then diluted with THF (1 mL, 0.1 M) and stirred for 1 h hour ensure the complete consumption of diazene. The 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 chromatography on silica gel (Et_2O/petroleum ether, typically 1:200) to give the desired product.

(*R*)-5-ethyl-2,4,5-triphenyl-4,5-dihydro-1,3,4-oxadiazin-6-one (**3aa**): 166 mg (93%), $R_f = 0.41$ (petroleum ether/diethyl ether, 50:1); white solid, mp 118–120 °C, $[\alpha]_D^{25} = -496.2$ deg cm^3 g^{-1} dm^{-1} (c = 0.5 g cm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$–7.77 (m, 2H), 7.37–6.95 (m, 13H), 2.98–2.86 (m, 1H), 2.50–2.38 (m, 1H), 0.82 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.8$, 144.5, 138.2, 137.6, 129.7, 129.4, 129.1, 128.7, 128.5, 128.3, 127.0, 125.2, 123.8, 122.0, 70.8, 27.4, 9.0 ppm; IR (KBr): $\tilde{\nu} = 3060$, 1777 (s, C=O), 1640 (m, C=N), 1596, 1494, 767, 759, 747 cm^{-1}; EIMS: m/z (%): 356 (37.0), 146 (100); HRMS (EI): m/z calcd for $C_{23}H_{20}N_2O_2$ [M^+]: 356.1525; found: 356.1527; HPLC analysis: 94% *ee* (Daicel CHIRALPAK AD-H column; 20 °C, 332 nm, 1.0 mL min^{-1}; solvent system: 2-propanol/hexane = 1:99; retention times: 6.4 min (minor), 12.9 min (major)).

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[11] Primitive investigations revealed that [2+2] cycloaddition product was also obtained for the reaction of ethylphenylketene with *N*,*N*′-diethoxycarbonyldiazene catalyzed by NHC. See the Supporting Information for details.

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[14] In addition to our report (reference [3a]), Enders et al. have also reported the synthesis of NHC precursor **4a** from L-pyroglutamic acid: D. Enders, J. Han, *Tetrahedron: Asymmetry* **2008**, *19*, 1367.

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[16] The possible involvement of aza-β-lactams as intermediates in the formation of 1,3,4-oxadiazin-2-ones is ruled out, based on the experiment that the ring expansion of the prepared aza-β-lactam to oxadiazin-2-one **3aa** is not observed under the optimized [4+2] cycloaddition reaction conditions.

[17] CCDC 703819 (**4a**), 703840 (**3da**) and 703841 (**7c**) 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.

