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Enantioselective [4+2] cycloaddition of ketenes and 9,10-phenanthrenequinone catalyzed by *N*-heterocyclic carbenes

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ABSTRACT

Chiral *N*-heterocyclic carbenes were found to be efficient catalysts for the formal [4+2] cycloaddition reaction of alkyl(aryl)ketenes and 9,10-phenanthrenequinone to give the corresponding cycloadducts in good yields with high enantioselectivities.

1. Introduction

Cycloaddition reactions of ketenes are powerful approaches for the synthesis of a diverse variety of cyclic compounds.[1] The enantioselective formal cycloaddition of ketenes via the zwitterionic enoate intermediates generated from ketenes and chiral Lewis base catalysts have been a very interesting and successful topic for decades since the Wynberg and Staring's pioneering report in 1982.[2] In addition to the well-developed enantioselective [2+2] cycloaddition of ketenes, the enantioselective [4+2] cycloaddition of ketenes has also attracted much attention. In 2006, Lectka and co-workers reported the first the cinchona alkaloid-catalyzed enantioselective formal [4+2] cycloaddition of ketenes and *o*-quinones, which could be an efficient entry to the chiral α-oxygenated carboxylic acid derivatives.[3a] Later on, the catalytic [4+2] cycloaddition reaction of ketenes with *o*-benzoquinone imides, *o*-benzoquinone diimides, and *N*-thioacyl with high enantioselectivities were developed by their and other groups.[3]

Recently, we successfully demonstrated that *N*-heterocyclic carbenes (NHCs)[4] could be efficient catalysts for the formal cycloadditions for ketenes with imines, 2-oxoaldehydes, diazenes, enones, and *o*-quinone methides.[5] It is interesting that compared to the cinchona alkaloids which are efficient catalysts for the cycloadditions of monosubstituted ketenes,[6] NHCs work very well for the reactions of disubstituted ketenes.[7] In this Letter, we wish to report a NHC-catalyzed [4+2] cycloaddition of disubstituted ketenes with 9,10-phenanthrenequinone to give the corresponding α,α-disubstituted α-oxygenated carboxylic acid derivatives.[8]

2. Results and discussion

Initially, the model reaction of ethyl(phenyl)ketene **5a** and *o*-chloranil **6** was investigated (Table 1). It was found that the chiral NHCs, generated freshly from the precursors (Fig. 1) in the presence of base,[9] could catalyze the reaction to give the [4+2] cycloaddition product in moderate to good yields with varied enantioselectivites. It is interesting that NHCs **2c–d** with a free hydroxyl group showed opposite enantioselectivities compared with NHCs **1a–e** with a protected hydroxyl group (entries 8, 16, and 17).[10] Reactions catalyzed by NHC **1a** in DCM gave the best result for the synthesis of cycloadduct **7**, while NHC **2d** and toluene are the conditions of choice for the synthesis of its enantiomer *ent*-**7** (entry 17). However, no satisfied yields and selectivities were reached by screening the catalysts, solvents, temperature and the bases. The uncatalyzed reactions, which could occur even in −78 °C (entry 18), may contribute to the low enantioselectivities of the reaction. Therefore, we turned to the substrates of less reactive *o*-quinones.

It was found that no reaction occurred for the mixture of ketene **5a** and 9,10-phenanthrenequinone without a catalyst, while 32% yield and 92% ee were realized for the reaction catalyzed by NHC **1a**′ (Table 2, entry 1).[11] Several series of NHCs were then tested for the model reaction (Table 2, entries 1–10). While NHC **1a**′ delivered the best enantioselectivity (entry 1), NHC **2c**′ was the choice for balancing the yield and enantioselectivity (entries 14 and 15).

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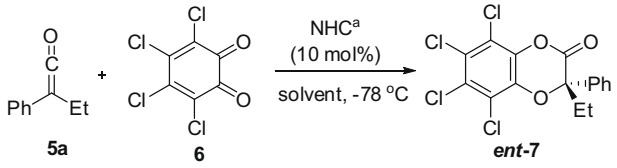
Table 1
Condition screening for the reactions of ketene **5a** and *o*-chloranil catalyzed by NHCs



Entry	NHC[a]	Solvent	Yield[b] (%)	ee[c,d] (%)
1[e]	**1a**′	THF	59	40
2	**1a**′	THF	64	69
3[f]	**1a**′	THF	48	76
4	**1b**′	THF	61	41
5	**1c**′	THF	48	0
6	**1d**′	THF	43	37
7	**1e**′	THF	45	21
8	**2c**′	THF	72	−5
9	**3**′	THF	95	−5
10	**4**′	THF	49	−9
11	**1a**′	Toluene	45	10
12	**1a**′	DCM	61	72
13	**1a**′[g]	THF	50	55
14	**1a**′[h]	THF	38	33
15	**2b**′	Toluene	30	0
16	**2c**′	Toluene	14	−43
17	**2d**′	Toluene	32	−72
18	None	THF	30	/

[a] NHCs **1**′–**4**′ were generated from their precursors **1**–**4** (10 mol %) and Cs_2CO_3 (10 mol %) or other noted base (entries 13 and 14) in the noted solvent at room temperature for 20–60 min, and used intermediately.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] The minus value indicates an opposite enantioselectivity observed.
[e] The ketene **5a** was added in one portion for entry 1, while added as its solution in 1 mL THF via a syringe pump over 1 h for other entries.
[f] The reaction was carried out at −100 °C (N_2(liq.)/EtOH bath).
[g] KOBu-*t* was used.
[h] DBU was used.

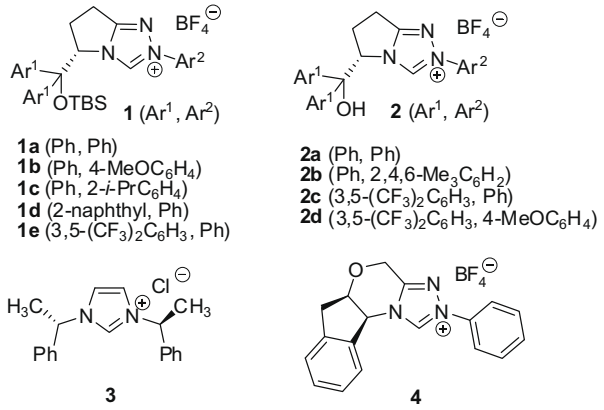
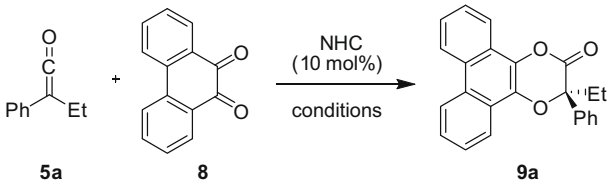


Figure 1. Structure of NHC precursors.

Further improvement was realized by the addition of 2.4 equiv of ketene in three portions (entries 14 and 15). 5 mol % loading of catalyst showed no change of enantioselectivity but resulted in a slightly lower yield (entry 16).

A variety of alkyl(aryl)ketenes were then tested for the reaction catalyzed by NHC **2c**′ (Table 3). Both alkyl(aryl)ketenes with electron-withdrawing (4-Cl, 4-Br) and electron-donating (4-Me, 4-MeO) substituents worked well (entries 2–5). Ketene **5f** with *meta*-chlorophenyl substituent gave products in low yield (entry 6). Interestingly, aryl(methyl)ketenes with unhindered aryl group, which showed very low enantioselectivities in Dochnahl and Fu's work,[7d] led to excellent enantioselectivities (entries 7–10). Ketenes

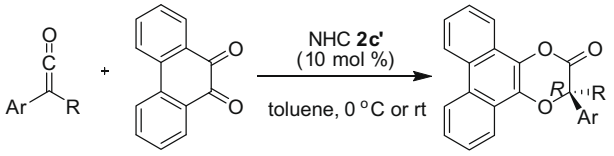
Table 2
Condition optimization for the reactions of ketene **5a** and 9,10-phenanthrenequinone



Entry	**5a**:**8**	NHC[a]	Conditions	Yield[b] (%)	ee[c] (%)
1	1.5:1	**1a**′	Toluene, rt	32	92
2	1.5:1	**1a**′	DCM, rt	58	76
3	1.5:1	**1b**′	Toluene, rt	22	88
4	1.5:1	**1c**′	Toluene, rt	18	66
5	1.5:1	**2a**′	Toluene, rt	23	53
6	1.5:1	**2b**′	Toluene, rt	9	−11[d]
7	1.5:1	**2c**′	Toluene, rt	44	87
8	1.5:1	**2d**′	Toluene, rt	15	48
9	1.5:1	**3**′	Toluene, rt	29	9
10	1.5:1	**4**′	Toluene, rt	31	−72[d]
11	2:1	**1a**′	Toluene, rt	44	82
12	2:1	**2c**′	Toluene, rt	34	88
13	2.4:1[e]	**1a**′	Toluene, rt	34	82
14	2.4:1[e]	**2c**′	Toluene, rt	95	91
15	2.4:1[e]	**2c**′	Toluene, 0 °C	95	92
16	2.4:1[e]	**2c**′[f]	Toluene, rt	82	91

[a] See note a in Table 1.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] The enantiomer of **9a** was obtained as the major product.
[e] After adding quinone **8**, ketene **5a** was added in three portion (3 × 0.8 equiv) in every 1 h.
[f] NHC **2c**′ (5 mol %) was used.

Table 3
Enantioselecitive [4+2] cycloaddition reaction catalyzed by chiral NHC **2c**′[a]



Entry	**5** (Ar, R)	**9**	Rt		0 °C	
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	**5a** (Ph, Et)	**9a**	95	91	95	92
2	**5b** (4-ClC_6H_4, Et)	**9b**[d]	83	91	97	93
3	**5c** (4-BrC_6H_4, Et)	**9c**	92	91	92	88
4	**5d** (4-MeC_6H_4, Et)	**9d**	91	88	90	93
5	**5e** (4-$MeOC_6H_4$, Et)	**9e**	96	85	86	90
6	**5f** (3-ClC_6H_4, Et)	**9f**	32	83	54	4
7	**5g** (Ph, Me)	**9g**	71	94	77	95
8	**5h** (4-ClC_6H_4, Me)	**9h**	75	91	76	79
9	**5i** (4-MeC_6H_4, Me)	**9i**	70	94	66	96
10	**5j** (4-$MeOC_6H_4$, Me)	**9j**	70	95	62	96
11	**5k** (Ph, *n*-Pr)	**9k**	98	76	74	86
12	**5l** (Ph, *n*-Bu)	**9l**	92	86	92	86
13	**5m** (4-ClC_6H_4, *i*-Pr)	**9m**	Trace	/	/	/
14	**5n** (2-naphthyl, Et)	**9n**	90	88	88	90
15	**5o** (Bn, Et)	**9o**	38	5	45	12

[a] See notes a and e in Table 2.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] The absolute stereochemistry of compound **9b** was determined by X-ray.

with long alkyl chains (*n*-Pr, *n*-Bu) worked well (entries 11 and 12), but ketenes with branched alkyl groups, such as isopropyl, did not work (entry 13). Reaction of ethyl(2-naphthyl)ketene gave product in 90% yields with 88% ee (entry 14). However, ethyl(benzyl)ketene

led to product in low yield with poor enantioselectivity (entry 15). The enantioselectivities could be improved by lowering reaction temperature to 0 °C for most cases except for reactions of ketenes **5c**, **5f**, and **5h** (entries 3, 6, and 8).[12]

In summary, chiral *N*-heterocyclic carbenes were found to be efficient catalysts for the formal [4+2] cycloaddition reaction of alkyl(aryl)ketenes and 9,10-phenanthrenequinone to give the corresponding cycloadducts in good yields with highly enantioselectivities. Further exploration on the enantioselective formal cycloaddition reactions of ketenes is underway in our laboratory.

3. Experimental section

3.1. Typical procedure for the [4+2] cycloaddition of ketenes with 9, 10-phenanthrenequinone catalyzed by NHC

To an oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with trazolium salt **2c** (36.4 mg, 0.05 mmol) and anhydrous Cs_2CO_3 (16.3 mg, 0.05 mmol). This tube was closed with a septum, evacuated, and back-filled with argon. To this mixture was added freshly distilled toluene (4 mL) and stirred for 20 min at room temperature. 9,10-Phenanthrenequinone **8** (104 mg, 0.5 mmol) was added in one portion, and ethyl(phenyl)ketene **5a** (58.5 mg, 64 μL, 0.4 mmol) was added via a syringe in three portion (3×0.4 mmol) in every 1 h. After the full conversion of 9,10-phenanthrenequinone, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography to give cycloadduct **9a** in 95% yield. White solid, $R_f = 0.5$ (petroleum ether/ethyl acetate = 20:1); mp 152–154 °C; $[\alpha]_D^{20}$ −146.2 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.63–8.61 (d, $J = 8.1$ Hz, 1H), 8.58–8.55 (d, $J = 9.1$ Hz, 1H), 8.49–8.46 (d, $J = 7.9$ Hz, 1H), 8.14–8.10 (m, 1H), 7.80–7.75 (m, 1H), 7.72–7.66 (m, 1H), 7.62–7.53 (m, 2H), 7.48–7.45 (m, 2H), 7.24–7.17 (m, 3H), 2.68–2.56 (m, 1H), 2.45–2.33 (m, 1H), 1.23–1.18 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 137.0, 133.0, 131.6, 128.8, 128.7, 128.4, 127.4, 127.3, 126.7, 125.8, 125.0, 124.9, 123.6, 122.9, 122.6, 121.5, 120.4, 84.4, 33.9, 8.21; IR (KBr) ν 3065, 2978, 1772 (s, C=O), 1338, 1132, 755, 723; EIMS *m/z*: 354 (20), 146 (100); HRMS-(EI) (*m/z*): M^+ calcd for $C_{24}H_{18}O_3$, 354.1256; found 354.1259; HPLC analysis: 91% ee [Daicel Chiralpak OD-H column; 20 °C, 254 nm, 1.0 mL/min; solvent system: 2-propanol/hexane = 10:90; retention times: 5.4 min (major), 12.4 min (minor)].

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and compounds characterization[13]) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.122.

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9. The bases, such as cesium carbonate, were found to be able to promote the cycloaddition reaction themselves. Thus the mixture of azolium salt and base was stirred for 20–60 min to make the full consumption of the base before the addition of substrates.
10. The enantioselectivity switch for cycloaddition reaction of ketenes and *N*-benzoyldiazenes catalyzed by NHC was reported in our previous publication (Ref. 5d).
11. The reaction of ketene **5a** and *o*-benzoquinone catalyzed by NHC **1a**′ gave a complex at room temperature, and no reaction occurred at −78 °C.
12. The reaction of (3-chlorophenyl)ethylketene (**5f**) at 0 °C went very slowly and it took 48 h instead of 2–8 h for other reactions. In this case, most of cycloadduct **9f** may be generated via the uncatalyzed or cesium carbonate-promoted reaction, and thus led to the extremely low ee for the whole reaction.
13. CCDC 754902 contains the Supplementary data for cycloadduct **9b** in this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.