

Asymmetric Dimerization of Disubstituted Ketenes Catalyzed by N-Heterocyclic Carbenes

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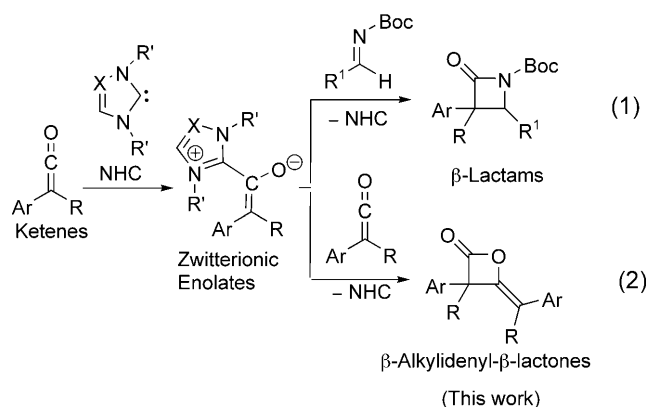
Abstract: A series of chiral N-heterocyclic carbenes (NHCs), derived from L-pyrogutamic acid, were found to be efficient catalysts for the asymmetric dimerization of alkylarylketenes to give the corresponding α -quaternary β -alkylidenyl- β -lactones in good yields with up to 97% *ee*. A chiral NHC with a proximal hydroxy group is superior in comparison with the corresponding NHC with its hydroxy group protected.

Keywords: asymmetric catalysis; carbenes; dimerization; ketenes; lactones

Introduced by Staudinger a century ago, ketenes are remarkable for the diverse range of useful products from their reactions.^[1] Being readily available, reactive and highly functionalized, diketene (4-methyleneoxetan-2-one) and its derivatives are very useful intermediates in organic synthesis.^[2] Calter et al. firstly reported the enantioselective dimerization of methylketene and other monosubstituted ketenes by employing *Cinchona* alkaloid derivatives as the catalysts.^[3] The resulting optically active β -alkylidenyl- β -lactones have been successfully utilized for the efficient synthesis of several intermediates and bioactive compounds.^[4] In comparison with monosubstituted ketenes, disubstituted ketenes are less reactive for the dimerization reaction. To the best of our knowledge, no enantioselective dimerization of disubstituted ketenes has yet been reported.^[5]

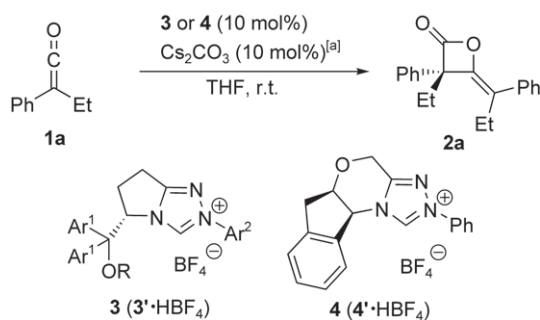
Recently, N-heterocyclic carbenes (NHCs) were found to be efficient organocatalysts for a wide variety of organic reactions.^[6] In the line with our research on NHC-catalyzed reactions,^[7] we proposed an activation mode of ketenes by N-heterocyclic carbenes to give zwitterionic enolates,^[8] and demonstrated that

NHCs were efficient catalysts for the formal cycloaddition reaction of disubstituted ketenes with imines to give the corresponding β -lactams in good yields with high enantioselectivities [Eq. (1)]. The successful activation of disubstituted ketenes by NHCs encouraged us to explore the enantioselective dimerization of disubstituted ketenes catalyzed by NHCs [Eq. (2)].



As expected, in the absence of catalyst, no dimerization reaction was observed for the solution of ethylphenylketene (**1a**) in THF at room temperature for 16 h. On the contrary, in presence of 10 mol% NHC **3a'**,^[7a,9] generated *in situ* from precursor **3a** and Cs_2CO_3 , the corresponding ketene dimer **2a** was obtained in 59% yield with 64% *ee* (Table 1, entry 1). NHC **3b'** with the bulkier *tert*-butyldimethylsilyl group catalyzed the reaction in very good yield (93%) but with similar *ee* (entry 2).

Recently, we found that the NHC with a proximal hydroxy group showed promising enantioselectivity in the aza-Mortia–Baylis–Hillman reaction of cyclopent-2-enone.^[10] Considering the possible H-bonding between the hydroxy group of the NHC and the substrate, NHC **3c'** with a proximal free hydroxy group

Table 1. Chiral NHCs screening for asymmetric ketene-dimerization.

Entry	3 (Ar ¹ , Ar ² , R)	Yield [%] ^[b]	ee [%] ^[c]
1	3a : Ph, Ph, TMS	59	64
2	3b : Ph, Ph, TBS	93	67
3	3c : Ph, Ph, H	43	77
4	3d : 2,5-(CF ₃) ₂ C ₆ H ₃ , Ph, H	47	91
5	3e : 2,5-(CF ₃) ₂ C ₆ H ₃ , Ph, TBS	34	88
6	3f : 2,5-(CF ₃) ₂ C ₆ H ₃ , 4-MeOC ₆ H ₄ , H	83	96
7	3g : Ph, 4-MeOC ₆ H ₄ , TBS	93	67
8	4	39	-50 ^[d]
9 ^[e]	3f	43	92
10 ^[f]	3f	26	90
11	3f (5 mol%), Cs ₂ CO ₃ (5 mol%)	62	95
12	3f (1 mol%), Cs ₂ CO ₃ (1 mol%)	42	94

^[a] The NHCs **3** and **4** were generated from the NHC precursor **3** and **4** (10 mol%) with Cs₂CO₃ (10 mol%) in THF at room temperature in 30 min and used immediately.

^[b] Isolated yields.

^[c] Determined by chiral HPLC.

^[d] *ent-2a* was obtained as the major enantiomer.

^[e] CH₂Cl₂ as the solvent.

^[f] Toluene as the solvent.

was then tested, and better enantioselectivity was observed (Table 1, entry 3). In order to increase the H-bond donating ability of the hydroxy group, strong electron-withdrawing substituents were introduced into the hydroxydiarylmethyl group and led to NHC precursor **3d**. It was found the reaction catalyzed by NHC **3d** gave the desired product with 91% *ee* albeit in only moderate yield (entry 4). The benefit of the free hydroxy group was further verified by comparison of the two reactions catalyzed by NHCs **3d** and **3e** (entry 4 vs. 5). Installing an electron-donating group in the *N*-aryl group may increase the nucleophilicity of the NHC, and thus NHC precursor **3f** was prepared. It turned out that the reaction catalyzed by NHC **3f** gave the ketene dimer **2a** in high yield and excellent enantioselectivity (entry 6). NHC **3g**, also bearing an electron-rich aryl group, afforded the reaction product in high yield with moderate enantioselectivity

(entry 7). The reaction catalyzed by tetracyclic NHC **4** gave the product with 50% *ee* (entry 8).

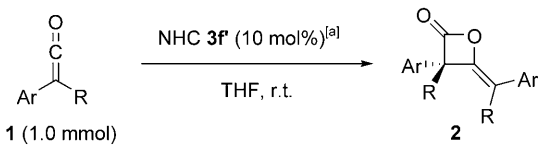
Solvent screening revealed that THF is better than dichloromethane and toluene (entries 6, 9 and 10). Decreasing the loading of NHC to 5 mol% and 1 mol% resulted in low yields but the high enantioselectivities were retained (entries 11 and 12).

With the optimal reaction conditions in hand, the scope of the NHC-catalyzed ketene dimerization was then investigated (Table 2). Methylphenylketene worked well but with somewhat decreasing enantioselectivity (84% *ee*) (entry 2). The reaction of phenylpropylketene (**1c**) gave the product with good enantioselectivity albeit in only moderate yield (entry 3). Both electron-donating groups (4-Me, 4-MeO) and electron-withdrawing groups (4-Cl, 4-Br) in the alkylarylketenes were tolerated, while electron-withdrawing groups showed some positive effect on the yields and enantioselectivities (entries 4–8). Ethyl(3-chlorophenyl)ketene (**1i**) worked well for the reaction, while ethyl(2-chlorophenyl)ketene (**1j**) did not (entry 9 vs. 10). It is interesting that the dimerization of ethyl(2-chlorophenyl)ketene (**1j**) occurred in the presence of catalytic NHC **3b** instead of **3f** albeit in low yield and with low enantioselectivity (entry 10 vs. 11). Scaling up the reaction to 5 mmol of ketene (**1h**) and using 6 mol% NHC resulted in little change in yields and an enantiomeric excess of 91% was achieved (entry 12). It is necessary to note that the reaction of dialkylketenes gave a complex mixture under the current reaction conditions.

Ketenes, generated in one pot from the corresponding acyl chloride in the presence of excess NEt₃, also worked for this NHC-catalyzed ketene dimerization reaction. For example, ethylphenylketene, generated from acyl chloride **6**, dimerized in the presence of 10 mol% NHC **3f** to give the corresponding product with high enantioselectivity albeit in moderate yield (Scheme 1).

The thus prepared β -alkenyl- β -lactones are highly functionalized compounds, and offer many possibilities for further chemical transformations (Scheme 2). For examples, the lactones (**2a**, **2f** and **2h**) could be reductively ring-opened by LiAlH₄ to give β -keto alcohols in good yields with excellent diastereoselectivities [Eq. (3)]. The reaction of alcohol **7h** with tosyl chloride afforded its tosylate **8**, whose absolute configuration was determined by X-ray studies [Eq. (4)]^[11]. The lactone could also be transformed to the ester by alcoholysis under basic or NHC-catalyzed conditions. However, no diastereoselectivity is observed for this alcoholysis reaction [Eq. (5)].

One possible catalytic cycle for this NHC-catalyzed reaction is depicted in Figure 1. An *N*-heterocyclic carbene attacks the α -carbon of the ketene to give a triazolium enolate **11**. The nucleophilic addition of enolate **11** to a second molecule of ketene generates

Table 2. Asymmetric ketene dimerization catalyzed by NHC **3f**.


Entry	1, 2 (Ar, R)	Time [h]	Yield [%] ^[b]	ee [%] ^[c]
1	a : Ph, Et	2	83	96
2	b : Ph, Me	2	72	84
3	c : Ph, <i>n</i> -Pr	2	56	92
4	d : 4-MeC ₆ H ₄ , Et	8	63	95
5	e : 4-MeOC ₆ H ₄ , Et	15	61	89
6	f : 4-ClC ₆ H ₄ , Et	2	99	94
7	g : 4-ClC ₆ H ₄ , <i>n</i> -Bu	5	71	97
8	h : 4-BrC ₆ H ₄ , Et	2	83	94
9	i : 3-ClC ₆ H ₄ , Et	3	70	96
10	j : 2-ClC ₆ H ₄ , Et	33	trace	–
11 ^[d]	j : 2-ClC ₆ H ₄ , Et	13	46	28
12 ^[e]	h : 4-BrC ₆ H ₄ , Et	2	89	91

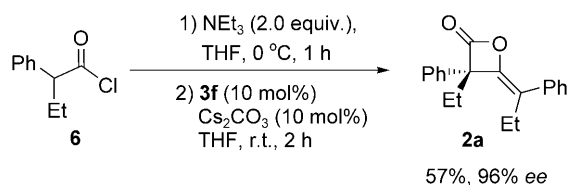
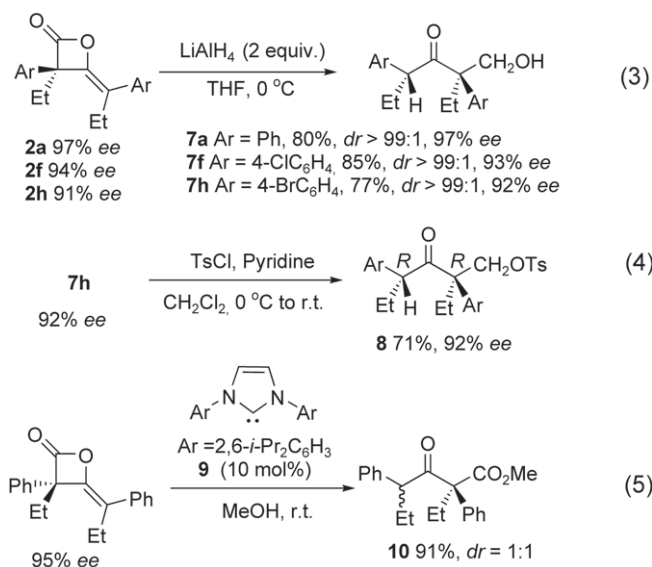
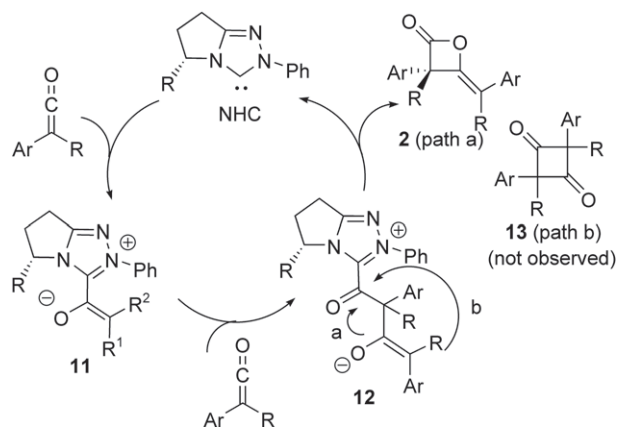
^[a] The NHC **3f** was generated from the precursor **3f** (10 mol%) with Cs₂CO₃ (10 mol%) in THF at room temperature in 30 min and used immediately.

^[b] Isolated yields.

^[c] Determined by chiral HPLC.

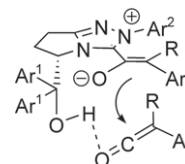
^[d] NHC precursor **3b** is used.

^[e] Ketene **1h** (5.0 mmol), **3f** (0.3 mmol), Cs₂CO₃ (0.3 mmol) were used.

**Scheme 1.** One-pot ketene generation and dimerization.**Scheme 2.** Chemical transformation of ketene dimers.**Figure 1.** Proposed catalytic cycle.

enolate **12**, which may collapse as *O*-nucleophile or *C*-nucleophile to give lactone **2** (path a) or diketone **13** (path b), respectively. It is interesting that diketone **13** is not observed in this NHC-catalyzed reaction, which may be due to steric repulsion between the two bulky groups of the triazolium and the alkylaryl *C*-nucleophile (path b).

Taking into consideration the dramatic effect of the proximal hydroxy group in the NHC on the enantioselectivity, a possible stereochemical model, which features an H-bonding between NHC and ketene is depicted in Figure 2.

**Figure 2.** Possible stereochemical model.

In conclusion, N-heterocyclic carbenes were found to be efficient catalysts for the dimerization of disubstituted ketenes. Good yields and high enantioselectivities were achieved for the reactions of a variety of alkylarylketenes catalyzed by a chiral NHC with a proximal hydroxy group. The resulting highly functionalized α -quaternary β -alkylidenyl- β -lactones may find applications in organic synthesis.

Experimental Section

General Procedure for the Asymmetric Dimerization of Ketenes Catalyzed by NHC

To the solution of NHC **3f**, which is generated freshly from the NHC precursor **3f** (76 mg, 0.1 mmol) and Cs₂CO₃ (32.6 mg, 0.1 mmol) in THF (4 mL) at room temperature for

30 min, was added ketene (1 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then filtered through a pad of silica gel and washed with ethyl acetate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) to give the desired product.

(S,Z)-3-Ethyl-3-phenyl-4-(1-phenylpropylidene)oxetan-2-one (2a): Yield: 129.4 mg (83%); $R_f=0.68$ (petroleum ether/ethyl acetate=20:1); colorless oil; $[\alpha]_D^{25}$: -23.7 (c 2.05, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta=7.17\text{--}7.41$ (m, 10H), 2.23–2.34 (m, 3H), 2.05–2.22 (m, 1H), 1.13 (t, $J=7.5$ Hz, 3H), 0.81 (t, $J=7.5$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta=170.8, 143.9, 135.3, 134.6, 129.2, 128.5, 128.5, 128.1, 127.5, 126.4, 116.4, 70.0, 26.2, 22.8, 12.7, 9.9$; IR (KBr, film): $\nu=2969, 1857, 1140, 914, 889, 696\text{ cm}^{-1}$; HR-MS-EI: $m/z=292.1467$ [M^+], calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_2$: 292.1463. HPLC analysis: 96% ee, [Daicel CHIRALPAK AD-H column; 20°C; 0.5 mL min $^{-1}$; solvent system: 2-propanol/hexane = 5:95; retention times: 8.6 min (minor), 10.3 min (major)].

Acknowledgements

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