DOI: 10.1002/adsc.200800532

Asymmetric Dimerization of Disubstituted Ketenes Catalyzed by N-Heterocyclic Carbenes

Hui Lv,[a] Yan-Rong Zhang,[a] Xue-Liang Huang,[a] and Song Ye[a,*]

[a] Beijing National Laboratory for Molecular Sciences, Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, People's Republic of China
Fax: (+86)-10-62554449; e-mail: songye@iccas.ac.cn

Received: August 26, 2008; Published online: November 14, 2008

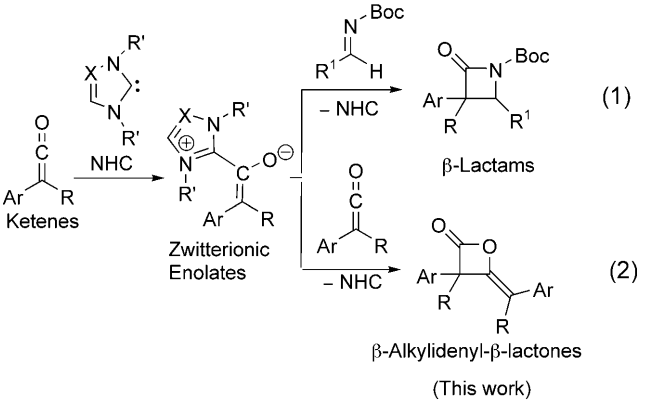
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800532.

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]

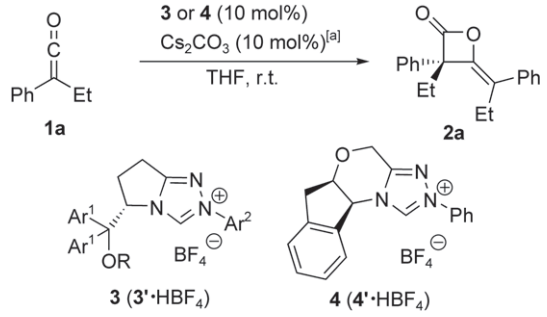
Recently, N-heterocyclic carbenes (NHCs) were found to be efficient organocatalysts for a wide variety of organic reactions.[6] In the line with our research on NHC-catalyzed reactions,[7] we proposed an activation mode of ketenes by N-heterocyclic carbenes to give zwitterionic enolates,[8] and demonstrated 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 disubstitued 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 enantioselecitvity 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-$(CF_3)_2C_6H_3$, Ph, H	47	91
5	**3e**: 2,5-$(CF_3)_2C_6H_3$, Ph, TBS	34	88
6	**3f**: 2,5-$(CF_3)_2C_6H_3$, 4-$MeOC_6H_4$, H	83	96
7	**3g:** Ph, 4-$MeOC_6H_4$, TBS	93	67
8	**4**	39	−50[d]
9[e]	**3f**	43	92
10[f]	**3f**	26	90
11	**3f** (5 mol%), Cs_2CO_3 (5 mol%)	62	95
12	**3f** (1 mol%), Cs_2CO_3 (1 mol%)	42	94

[a] The NHCs **3′**and **4′** were generated from the NHC precursor **3** and **4** (10 mol%) with Cs_2CO_3 (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] CH_2Cl_2 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 introducted 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 compasion 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 nucleophility 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).

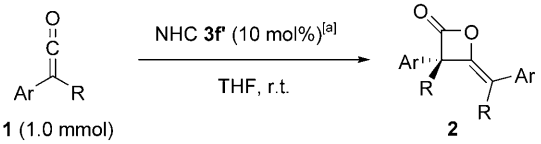
With the optimal reaction conditions in hand, the scope of the NHC-catalyzed ketene dimerization was then investigated (Table 2). Methylphenylketene worked well but with somewhat decreasing enantioselectivity (84% *ee*) (entry 2). The reaction of phenylpropylketene (**1c**) gave the product with good 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 enantioselecitvities (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 enantiomerical 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 NEt_3, 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 $LiAlH_4$ 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)].

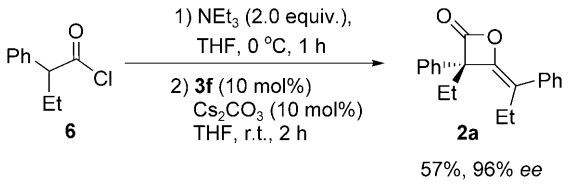
One possible catalytic cycle for this NHC-catalyzed reaction is depicted in Figure 1. An N-heterocyclic carbene attacks the α-carbon of the ketene to give a triazolium enolate **11**. The nucleophilic addition of enolate **11** to a second molecule of ketene generates

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

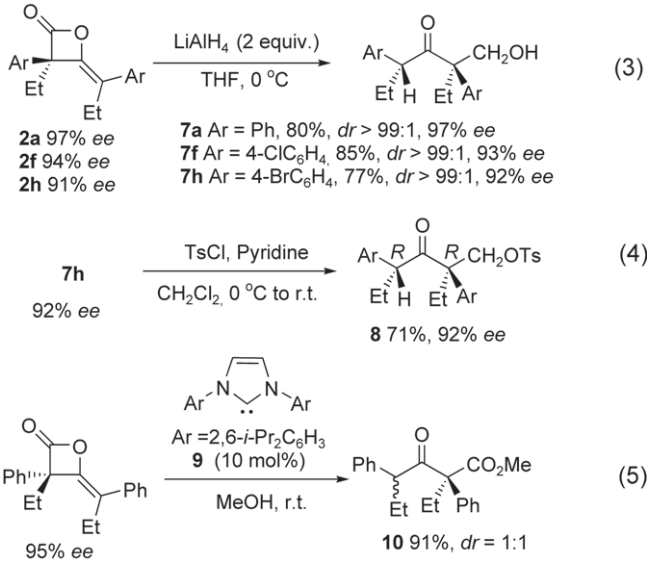


Entry	**1, 2** (Ar, R)	Time [h]	Yield [%][b]	*ee* [%][c]
1	**a**: Ph, Et	2	83	96
2	**b**: Ph, Me	2	72	84
3	**c**: Ph, *n*-Pr	2	56	92
4	**d**: 4-MeC_6H_4, Et	8	63	95
5	**e**: 4-MeOC_6H_4, Et	15	61	89
6	**f**: 4-ClC_6H_4, Et	2	99	94
7	**g**: 4-ClC_6H_4, *n*-Bu	5	71	97
8	**h**:4-BrC_6H_4, Et	2	83	94
9	**i**: 3-ClC_6H_4, Et	3	70	96
10	**j**: 2-ClC_6H_4, Et	33	trace	–
11[d]	**j**: 2-ClC_6H_4, Et	13	46	28
12[e]	**h**: 4-BrC_6H_4, Et	2	89	91

[a] The NHC **3f′** was generated from the precursor **3f** (10 mol%) with Cs_2CO_3 (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), Cs_2CO_3 (0.3 mmol) were used.



Scheme 1. One-pot ketene generation and dimerization.



Scheme 2. Chemical transformation of ketene dimers.

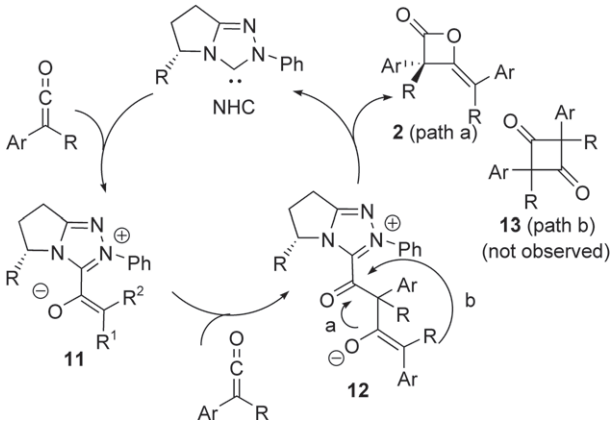


Figure 1. Proposed catalytic cycle.

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.

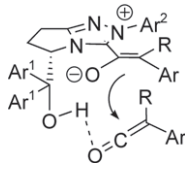


Figure 2. Possible stereochemical model.

In conclusion, N-heterocyclic carebenes 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 Cs_2CO_3 (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}H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$–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}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 cm^{-1}; HR-MS-EI: $m/z = 292.1467$ [M$^+$], calcd. for $C_{20}H_{20}O_2$: 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

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

References

[1] a) T. T. Tidwell, *Ketenes* 2nd edn., John Wiley & Sons, Hoboken, New Jersey, **2006**; b) T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 5926; *Angew. Chem. Int. Ed.* **2005**, *44*, 5778; c) T. T. Tidwell, *Eur. J. Org. Chem.* **2006**, 563; d) R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545.

[2] R. J. Clemens, *Chem. Rev.* **1986**, *86*, 241.

[3] a) M. A. Calter, *J. Org. Chem.* **1996**, *61*, 8006; b) M. A. Calter, R. K. Orr, W. Song, *Org. Lett.* **2003**, *5*, 4745.

[4] a) M. A. Calter, X. Guo, *J. Org. Chem.* **1998**, *63*, 5308; b) M. A. Calter, F. C. Bi, *Org. Lett.* **2000**, *2*, 1529; c) M. A. Calter, X. Guo, W. Liao, *Org. Lett.* **2001**, *3*, 1499; d) M. A. Calter, W. Liao, *J. Am. Chem. Soc.* **2002**, *124*, 13127; e) R. J. Duffy, K. A. Morris, D. Romo, *J. Am. Chem. Soc.* **2005**, *127*, 16754; f) V. C. Purohit, R. D. Richardson, J. W. Smith, D. Romo, *J. Org. Chem.* **2006**, *71*, 4549.

[5] For asymmetric reactions of disubstituted ketenes other than dimerization, see: a) B. L. Hodous, J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 2637; b) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586; c) C.-Y. Li, X.-L. Sun, Q. Jing, Y. Tang, *Chem. Commun.* **2006**, 2980.

[6] For the reviews of NHC-catalyzed reactions, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; c) K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; d) M. Christmann, *Angew. Chem.* **2005**, *117*, 2688; *Angew. Chem. Int. Ed.* **2005**, *44*, 2632; e) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534.

[7] a) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277; b) Y.-R. Zhang, H. Lv, D. Zhou, S. Ye, *Chem. Eur. J.* **2008**, *14*, 8473.

[8] Smith et al. have simultaneously reported their results of the NHC-catalyzed formal cycloaddition of disubstituted ketenes with imines: N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108.

[9] Enders et al. have simultaneously reported the synthesis of NHC precursor **3a**, **b** from L-pyroglutamic acid: D. Enders, J. Han, *Tetrahedron: Asymmetry.* **2008**, *19*, 1367.

[10] a) L. He, Y.-R. Zhang, X.-L. Huang, S. Ye, *Synthesis* **2008**, 2825; b) L. He, T.-Y. Jian, S. Ye, *J. Org. Chem.* **2007**, *72*, 7466.

[11] CCDC 699375 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.

