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Chiral *N*-Heterocyclic Carbene-Catalyzed Formal [4+2] Cycloaddition of Ketenes with Enones: Highly Enantioselective Synthesis of *trans*- and *cis*-δ-Lactones

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Introduced by Staudinger a century ago, ketenes are remarkable for the diverse range of useful products from their reactions.[1] In 1982, Wynberg et al. reported the cinchona alkaloid-catalyzed ketene–chloral cycloadditions to give the corresponding β-lactones with up to 98% *ee*.[2] After that, catalytic asymmetric ketene dimerizations,[3] ketene–aldehyde cycloadditons,[4] and ketene–imine cycloadditions[5] have been developed. In comparison with these [2+2] ketene cycloadditions, the enantioselective [4+2] ketene cycloadditions are far less established. Evans et al. reported the high enantioselective [4+2] cycloaddition of a silylketene with an enone catalyzed by a bis(oxazoline)–copper complex, but only one example was shown.[4c] Very recently, the cinchona alkaloid-catalyzed reaction of ketenes with *o*-benzoquinones, *o*-benzoquinone imides, *o*-benzoquinone diimides,[6] and *N*-thioacyl imines[7] to give the corresponding [4+2] cycloaddition products with high enantioselectivities were developed by Lectka et al. and Nelson et al., respectively. And the [4+2] cycloaddition of vinylketenes with aldehydes to give δ-lactones was achieved by Peters et al.[8]

Recently, *N*-heterocyclic carbenes were found to be efficient catalysts for the umpolung of aldehydes, a^3 to d^3 umpolung of enals, aza-Morita–Baylis–Hillman reaction, transesterification, acylation, ring-opening polymerization, activation of silylated nucleophiles and other reactions.[9] In our previous publication, we proposed an activation mode of ketenes by NHCs to give zwitterionic enolates, and demonstrated that NHCs were efficient catalysts for the cycloaddition of ketenes with imines.[10] In this communication, we wish to report the chiral NHCs-catalyzed formal [4+2] cycloaddition of ketenes with enones to give δ-lactones, which are the key motifs for a wide range of bioactive compounds and versatile intermediates in organic synthesis.[11] Very recently, Bode et al. developed an elegant chiral NHCs-catalzyed [4+2] cycloaddition of α-chloroaldehydes with enones to give δ-lactones.[12] Our [4+2] cycloaddition of disubstituted ketenes[13] with enones led to the highly functionalized δ-lactones with α-quaternary-β-tertiary stereocenters[14,15]

Chiral NHC precursor **1**, easily prepared from L-pyroglutamic acid,[10] was employed for the reaction of ethylphenylketene (**2a**) with enone **3a**. It was found that 10 mol% precatalyst **1**, in the presence of Cs_2CO_3 (10 mol%), could catalyze the reaction to give the corresponding δ-lactone **4a** in 55% yield with 10:1 diastereoselectivity and 84% *ee* for the *trans*-isomer and 80% *ee* for the *cis*-isomer (Table 1, entry 1). When the reaction was carried out at −20°C, the enantioselectivity was increased to 89% *ee*, while the yield and diastereoselectivity dropped sharply (entry 2). Careful experiments revealed that *cis*-isomer of lactone **4a** could be epimerized to *trans*-isomer in the conditions of cycloaddition.[16] Thus, an excess of the base of Cs_2CO_3 (20 mol%) was employed, and the *trans*-isomer of δ-lactone **4a** was obtained with high diastereomeric purity (entry 3).

Further experiments showed that the yields were increased when the reactions were carried out by slow addition of ketenes (entries 4–5). Reaction at 0°C led to better enantioselectivity and yield, while reaction at −10°C resulted in slightly better enantioselectivity with compromised yield (entry 6). It is noteworthy that lactone **4a** with *trans*/*cis* 24:1 and 91% *ee* could be easily recrystallized from hexane/2-propanol 9:1 to give pure *trans*-isomer in 70% yield with 98% *ee*.

Substrate investigations revealed a variety of ketenes and enones worked well in the NHC-catalyzed cycloadditions (Table 2). Both arylenones with electron-withdrawing group (4-Cl, 4-BrC_6H_4 and 4-$NO_2C_6H_4$) and those with electron-donating group (4-Me) are suitable substrates, furnishing δ-lactones in good yields with high enantioselectivities (entries 2–5). Heteroarylenone (R^3=2-furyl) and bulky arylenone (R^3=β-naphthyl) reacted with no notable difference

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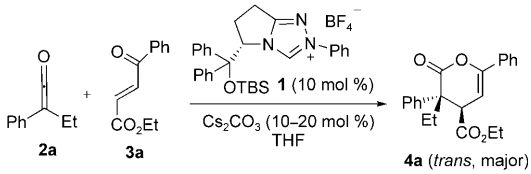
Table 1. Optimization of conditions.[a]



Entry	Cs_2CO_3 [mol %]	Conditions	Yield [%][b]	*trans*/*cis*[c]	*ee* (*trans*, *cis*) [%][d]
1	10	RT, 2 h	55	10:1	84, 80
2	10	−20 °C, 12 h	10	3:1	89, 69
3	20	RT, 2 h	51	22:1	84, 84
4[e]	20	RT, 2 h	73	20:1	86, 88
5[e]	20	0 °C to RT[f]	79	24:1	91, 88,
6[e]	20	−10 °C to RT[f]	28	32:1	91, 93

[a] Ketene **2a** (1.5 mmol), enone **3a** (1.0 mmol) was employed. [b] Isolated yields. [c] Determined by ^1H NMR (300 MHz) and/or HPLC. [d] Determined by HPLC on chiral columns. [e] The solution of ketene **2a** in THF (2.5 mL) was added over 1 hour. [f] After the addition of ketene **2a** over 1 hour, the reaction mixture was stirred for 30 min at 0 °C or −10 °C, then was allowed to warm to RT and stirred for 24 h.

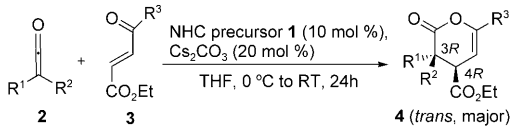
in yields and selectivities (entries 6 and 7). Arylalkylketenes with electron-withdrawing groups worked well with enones furnishing δ-lactones in good yields and high enantioselectivites (entries 8 and 9), while the one with electron-donating group, 4-methoxylphenylethylketene, resulted in fair yields[17] but high enantioselectivity (entry 10). The reaction of phenylmethylketene afforded exclusively *trans*-isomer with 84% *ee* (entry 11). It should be noted that the reaction of monosubstituted ketenes under current reaction condition failed to give the δ-lactones but a complex mixture. It is noteworthy that the diastereomeric ratios and enantiomeric excess could be further improved by a single recrystallization from hexane/2-propanol 9:1.

Since the *trans*-isomer of δ-lactones were obtained as major product through the in situ epimerization of *cis*-isomer in the thermodynamically-controlled conditions, it will be quite useful if the *cis*-isomer could be obtained predominately by kinetically controlled conditions. Indeed, the *cis*-isomer was successfully obtained by deprotonation of *trans*-isomer of the δ-lactones, followed by kinetically controlled protonation of the resulting carbanion at −78 °C (Scheme 1).

The *cis*-isomer of δ-lactones could also be obtained in good yield with high diastereoselectivity and enantioselectivity by in situ deprotonation-protonation after the NHC-catalyzed cycloaddition (Scheme 2). Both electron-donating and electron-withdrawing substituents at the *para*-position of the aryl group (**4h-c**, **4l-c**) are tolerated; and the *meta*-substituent (2-Cl) has no notable effect for the reaction (**4m-c**).

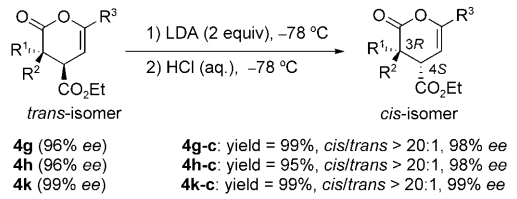
Ketenes generated in situ from the corresponding acyl chloride in the presence of excess NEt_3 also worked well for this NHC-catalyzed ketene–enone cycloaddition reaction, but longer reaction times are required for full conversion of enones. For example, ketene **2a**, generated from acyl chloride **5**, reacted with enone **3a** to give δ-lactone in 77% yield with 88% *ee* (Scheme 3).

Table 2. Synthesis of *trans*-δ-lactones by NHC-catalyzed ketene–enone cycloaddition.[a]

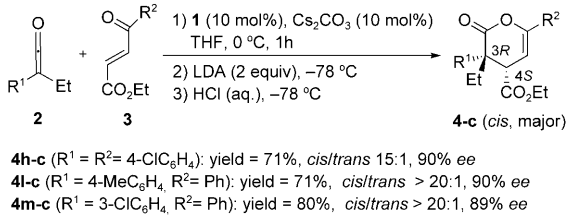


Entry	R^1, R^2	R^3	**4**	Yield [%][b,c]	*trans*/*cis*[d,e]	*ee* [%][f–h]
1	Ph, Et	Ph	**4a**	79 (70)	24:1	91 (98)
2	Ph, Et	4-ClC_6H_4	**4b**	70 (59)	18:1	90 (99)
3	Ph, Et	4-BrC_6H_4	**4c**	68 (52)	22:1	87 (98)
4	Ph, Et	4-$NO_2C_6H_4$	**4d**	61 (50)	20:1	91 (97)
5	Ph, Et	4-MeC_6H_4	**4e**	69 (54)	25:1	90 (97)
6	Ph, Et	2-furyl	**4f**	78 (15)	39:1	92 (95)
7	Ph, Et	β-naphthyl	**4g**	82 (76)	25:1	90 (95)
8	4-ClC_6H_4, Et	4-ClC_6H_4	**4h**	74 (61)	15:1	89 (99)
9	4-ClC_6H_4, Et	Ph	**4i**	93 (63)	17:1	91 (90)
10	4-$MeOC_6H_4$, Et	Ph	**4j**	57 (64)	16:1	91 (99)
11	Ph, Me	4-ClC_6H_4	**4k**	82 (63)	>99:1	84 (99)

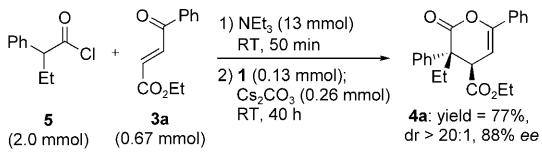
[a] Ketene **2** (1.5 mmol), enone **3** (1.0 mmol) was employed. [b] Isolated yields. [c] The yields of recrystallization were shown in parentheses. [d] Determined by HPLC. [e] Only *E* isomers or *E*/*Z*> 99:1 was observed after recrystallization. [f] Determined by HPLC on chiral columns. [g] The ees after recrystallization are shown in parentheses. [h] The absolute configuration of lactone **4h** was determined by X-ray, and that of other lactones was assigned by comparison of their specific rotation with the specific rotation of **4h**.



Scheme 1. Synthesis of *cis*-δ-lactones from *trans*-δ-lactones.



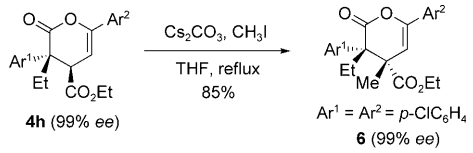
Scheme 2. Synthesis of *cis*-δ-lactones from ketene–enone cycloaddition.



Scheme 3. In situ generation of ketene from acyl choride.

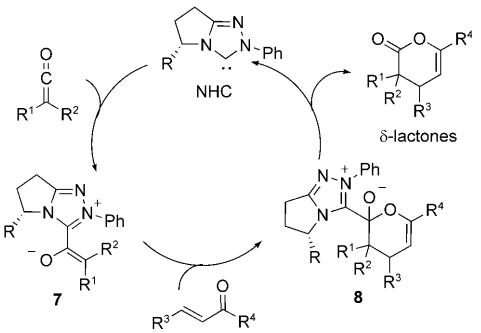
The β-carbonyl group in lactone **4** offer many possibilities for further transformation. For example, lactone **4h** could easily be alkylated at the β-position to give δ-lactone **6** with two contiguous quaternary stereocenters. Similarly to the ki-

netically controlled protonation, the stereochemistry in β-carbon was reversed, and the *cis*-isomer was obtained exclusively without erosion of enantiopurity (Scheme 4).



Scheme 4. β-Alkyation of δ-kactone.

This NHC-catalyzed [4+2] cycloadditions of ketenes are possibly initiated by the nucleophilic addition of NHC to ketenes to give triazolium enolates **7**, which react with enones by an inverse electron demand Diels–Alder reaction to give the [4+2] cycloaddition adducts **8**, followed by elimination of NHC to furnish the corresponding δ-lactones **4** and regenerate the NHC catalyst (Scheme 5).[18]



Scheme 5. Proposed mechanism.

In conclusion, the chiral NHC **1** was demonstrated as an efficient catalyst for the formal [4+2] cycloaddition of disubstituted ketenes with enones to give δ-lactones with α-quaternary-β-tertiary stereocenters. Both the *trans*-isomers and the *cis*-isomers of the δ-lactones could be obtained in good yields with high diastereo- and enantioselectivities by in situ thermodynamically controlled epimerization and kinetically controlled protonation, respectively. Ketene generated in situ from acyl chloride also worked well for the reaction. Further exploration of the NHC-catalyzed ketene cyclization reactions is underway in our laboratory.

Experimental Section

Synthesis of *trans*-δ-lactones 4 (Table 2): A mixture of NHC percursor **1** (60 mg, 0.1 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) in THF (2 mL) was stirred at room temperature for 10 min. The resulting solution was cooled to 0 °C, and enone (1.0 mmol) was added in one portion, followed by slow addition of the solution of ketene (1.5 mmol) in 2.5 mL THF via syringe pump over 1 h. After the full conversion of enone, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography to give *trans*-isomer of δ-lactones **4** as the major product, which was recrystallized from hexane/2-propanol 9:1 to give nearly pure *trans*-isomer. Lactone **4h**: White solid; Yield: 74%; R_f = 0.35 (petroleum ether/EtOAc 9:1); m.p. 151–152 °C; $[\alpha]_D^{25} = -196.4$ (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.7 Hz, 2H), 7.30–7.15 (m, 6H), 5.78 (d, J = 7.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.93 (d, J = 7.1 Hz, 1H), 2.30–2.20 (m, 1H), 2.00–1.85 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.70 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.14, 169.61, 151.06, 135.39, 134.84, 133.72, 129.81, 128.86, 128.57, 127.99, 125.95, 97.42, 61.88, 50.46, 45.19, 29.18, 13.92, 7.86 ppm; IR (KBr film): ν = 2975, 1752, 1723, 1493, 1331, 1200, 1145, 1009, 826 cm^{-1}; HRMS (EI): m/z: calcd for: 418.0739, found 418.0737 $[M]^+$; elemental analysis calcd (%) for $C_{22}H_{20}O_4Cl_2$: C 63.02, H 4.81, N 0.00; found: C 63.21, H 4.73, N < 0.30; HPLC analysis: 89% *ee* (99% *ee* after recrystallization), [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: isopropanol/hexanes 10:90; t_R = 9.5 min (minor), 11.5 min (major)].

Synthesis of *cis*-δ-lactones 4-c (Scheme 2): The cycloaddition of ketenes (1.5 mol) and enones (1.0 mol) was carried out as the procedure of synthesis of *trans*-δ-lactones with Cs_2CO_3 (33 mg, 0.1 mmol). After the full conversion of enone, the reaction mixture was cooled to −78 °C, and LDA (2.0 M in THF, 1.0 mL) was added dropwise. After stirring for 8 h, the reaction mixture was acidified by HCl (1.0 M, aq) to pH 2.0 at −78 °C. The solution was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4, followed by concentration under reduced pressure. The residue was purified by flash column chromatography to give *cis*-δ-lactones as the major product. Lactone **4h-c**: white solid; Yield: 71%; R_f = 0.35 (petroleum ether/EtOAc 9:1); m.p. 48–50 °C; $[\alpha]_D^{25}$ = +255.1 (c = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H), 7.30–7.15 (m, 4H), 5.79 (d, J = 6.4 Hz, 1H), 3.90–3.80 (m, 4H), 2H), 3.56 (d, J = 6.4 Hz, 1H), 2.20–2.00 (m, 2H), 0.95 (t, J = 7.1 Hz, 3H), 0.72 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.00, 167.44, 150.50, 135.83, 135.64, 133.39, 130.01, 129.40, 128.83, 128.30, 126.13, 96.96, 61.60, 50.44, 45.19, 29.77, 13.73, 8.64 ppm; IR (KBr film): ν = 1771, 1731, 1492, 1187, 1093, cm^{-1}; HRMS (EI): m/z: calcd for $C_{22}H_{20}O_4Cl_2$: 418.0739, found 418.0742 $[M]^+$; HPLC analysis: 90% *ee*, [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL min^{-1}; solvent system: isopropanol/hexanes 10:90; t_R = 23.6 min (minor), 29.7 min (major)].

Acknowledgements

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Keywords: asymmetric catalysis · carbenes · cycloaddition · ketenes · lactones

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[16] See Supporting Information for details.

[17] The low yields of several cases may be caused by the decomposition of the ketene and/or the enone in the reaction condition.

[18] Another possible mechanism is the Michael addition of triazolium enolate to enones, followed by intramolecular cyclization to give δ-lactones.

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