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Formal Cycloaddition of Disubstituted Ketenes with 2-Oxoaldehydes Catalyzed by Chiral N-Heterocyclic Carbenes

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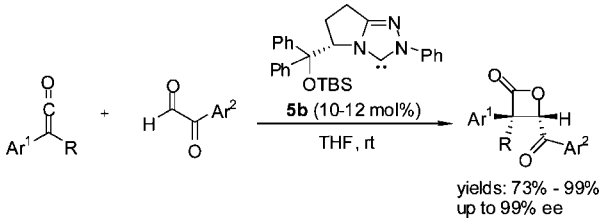
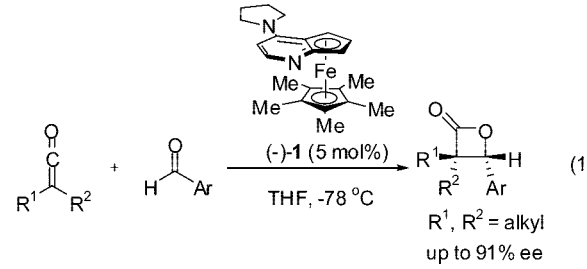


Chiral N-hetereocyclic carbenes were found to be efficient catalysts for the formal [2 + 2] cycloaddition reactions of alkyl(aryl)ketenes with 2-oxoaldehydes to afford β-lactones with α-quaternary-β-tertiary stereocenters in high yields with good diastereoselectivities and excellent enantioselectivities (up to 99% ee). Both alkyl(aryl)ketenes and diarylketene worked well in this reaction.

The asymmetric [2 + 2] cycloaddition of ketenes with aldehydes to construct optically active β-lactones has been continuously pursued for decades.[1] Chiral Lewis bases, Lewis acids, and bifunctional catalysts have been employed for this process. In 1982, Wynberg et al. published their pioneering work of the highly enantioselective cinchona alkaloid-catalyzed formal cycloaddition of unsubstituted ketene (CH_2=C=O) with chloral.[2] The asymmetric reaction of unsubstituted ketene with a variety of aldehydes was then achieved by using an aluminum−triamine complex catalyst,[3] chiral oxazaborolidine catalyst,[4] and Lewis acid−Lewis base bifunctional catalyst.[5] Bis(oxazoline)−copper complexes were demonstrated to be efficient catalysts for the reaction of silylketene (TMSCH=C=O) with chelating carbonyl substrates.[6] Alkylketenes were found to be more challenged substrates than unsubstituted ones for this formal cycloaddition reaction.[7] In this context, a strategy of combination of cinchona alkaloid as Lewis base and lithium perchlorate or lanthamide triflates as Lewis base was successfully employed.[8] The intramolecular version of this reaction was also realized by employing *O*-acetyl quinidine as catalyst.[9]

Disubstituted ketenes are less reactive and become the most challenging substrate for this process.[10] Remarkably, Fu et al. reported that planar-chiral 4-pyrrolidin-1-ylpyridine (**1**) was an efficient catalyst for the formal cycloaddition of disubstituted ketenes with aldehydes to furnish β-lactones in good yields with excellent enantioselectivities (up to 91% ee) (eq 1).[11] Although this catalytic system worked very well for dialkylketenes, it failed for alkyl(aryl)ketenes.



Recently, N-heterocyclic carbenes (NHCs) were found to be efficient organocatalysts for the umpolung of aldehydes for benzoin reaction and Stetter reaction,[12] extended umpolung of functional aldehydes,[13] intramolecular β-alkylation of Michael acceptors,[14] aza-Mortia−Baylis−Hillman reaction[15] and many other reations.[16]

Smith et al. and our group have independently reported that NHCs were efficient catalysts for the formal cycloaddition of

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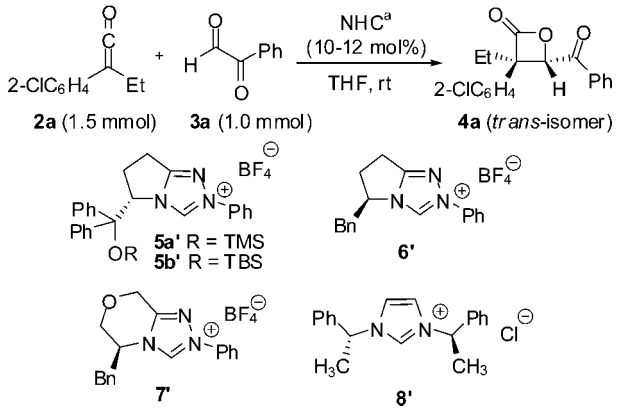
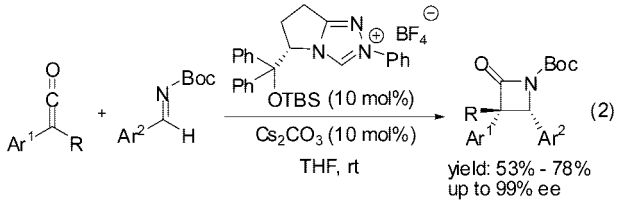
TABLE 1. Chiral NHCs for the Formal Cycloaddtion of Ketene 2a with 2-Oxoaldehyde 3a



entry	NHC[a]	yield (%)[b]	dr[c]	ee (%)[d]
1	**5a**	75	>20:1	89
2	**5b**	85	>20:1	97
3	**6**	69	>20:1	−24[e]
4	**7**	76	>20:1	−58[e]
5	**8**	60	>20:1	4

[a] NHCs **5**−**8** were generated from NHC precursors **5′**−**8′** (12 mol %) with Cs_2CO_3 (10 mol %) in THF at room temperature in 1 h and used immediately. [b] Isolated yields. [c] Determined by ^{1}H NMR (300 MHz), with only trace *trans*-isomers detected. [d] Determined by HPLC on Daicel Chiralpak As−H column. [e] ***ent*-4a** was the major product.

disubstituted ketenes with imines (eq 2).[17] Thus, it is quite interesting for us to explore the NHC-catalyzed formal cycloaddition of alkyl(aryl)ketenes with aldehydes to give β-lactones bearing α-quaterary-β-tertiary stereocenters.[18]



Unfortunately, initial experiments showed that the formal cycloaddition reaction of ethyl(2-chlorophenyl)ketene (**2a**) with 4-chlorobenzaldehyde did not occur in the presence of achiral or chiral NHCs (10−20 mol %), and ^{1}H NMR showed that most ketene and aldehyde remained unchanged.

2-Oxoaldehydes, which are more active than normal aldehydes and represent an important substance class as versatile building blocks in organic synthesis, were then explored. It was found that NHC **5a**,[19] generated from the corresponding precursor **5a′** with Cs_2CO_3, could catalyze the cycloaddition reaction of ketene **2a** with 2-oxo-2-phenylacetaldehyde at room temperature to afford the corresponding β-lactones in 75% yield with highly diastereo- and enantioselectivity (dr = 20:1, 89% ee) (Table 1, entry 1). An enantiomerical excess of 97% was

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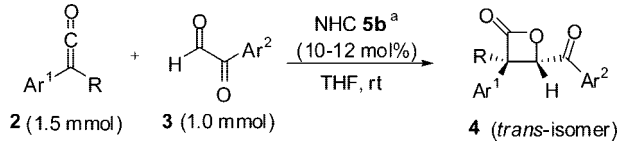
TABLE 2. Cycloaddition Reaction of Disubstituted Ketenes with 2-Oxoaldehydes Catalyzed by NHC 5b



entry	**2**: Ar^1, R	**3**: Ar^2	**4**	dr[b]	yield (%)[c]	ee (%)[d]
1	2-ClC$_6$H$_4$, Et	Ph	**4a**	>20:1[e]	85	97
2	2-ClC$_6$H$_4$, Et	4-MeOC$_6$H$_4$	**4b**[f]	>20:1[e]	98	99[g]
3	2-ClC$_6$H$_4$, Et	4-BrC$_6$H$_4$	**4c**	*h*	99	99[g]
4	2-ClC$_6$H$_4$, Et	1-naphthyl	**4d**	10:1	65	95
5	2-ClC$_6$H$_4$, Et	2-naphthyl	**4e**	*h*	88	97
6	4-ClC$_6$H$_4$, ^{i}Pr	Ph	**4f**	4:1[i]	76	99[g]
7	4-ClC$_6$H$_4$, ^{i}Pr	4-MeC$_6$H$_4$	**4g**	4:1[i]	77	94
8	Ph, ^{i}Pr	Ph	**4h**	4:1[i]	76	99[g]
9[j]	Ph, ^{i}Pr	Ph	**4h**	4:1[i]	73	98
10	Ph, Ph	Ph	**4i**		99	78
11	(CH$_2$)$_6$	Ph	**4j**		63	4
12	2-ClC$_6$H$_4$, ^{i}Pr	benzyl			*k*	

[a] NHC **5b** was generated from the precursor **5b′** (12 mol %) with Cs_2CO_3 (10 mol %) in THF at room temperature in 1 h and used immediately. [b] Determined by ^{1}H NMR (300 MHz) of the reaction mixture. [c] Isolated yields of pure *trans*-isomers. [d] Determined by HPLC on Chiral Column. [e] Only trace *cis*-isomer detected. [f] The absolute configuration of lactone **4b** was determined by X-ray to be (3*R*,4*S*), and the configuration of other lactones was determined by comparison of its specific rotation and CD sepectrum with those of lactone **4b**. [g] Only one enantiomer detected by HPLC. [h] *trans* only. [i] Yields and ee's of the *cis*-isomers: **4f-*cis*** (23%, 65% ee), **4g-*cis*** (20%, 65% ee), **4h-*cis*** of entry 8 (22%, 13% ee), **4h-*cis*** of entry 9 (23%, 13% ee). [j] The reaction was carried out at 0 °C. [k] No reaction.

then achieved by employing catalyst NHC **5b** with a bulky *tert*-butyldimethylsilyl substituent (entry 2). Several other NHCs (**6**−**8**) were also tested, and low to moderate enantioselectivities were resulted (entries 3−5).

The scope of the reaction is showed by the use of a variety of ketenes and aldehydes in this cycloaddition reaction (Table 2). Both 2-oxo-2-arylacetaldehydes with an electron-donating substituent (4-MeO) and with an electron-withdrawing substituent (4-Br) worked very well and afforded the corresponding β-lactone in high yields with excellent diastereo- and enantioselectivities (entries 2 and 3). Aldehydes with bulky aryl groups (1- and 2-naphthyl) also worked well (entries 4 and 5). The reactions of aryl(isopropyl)ketenes went smoothly. Though the diastereoselectivities dropped to 4:1, the excellent enantioselectivities were kept in these cases (entries 6−8). Lowering the reaction temperature to 0 °C had no beneficial effect on the yield and selectivity of the reaction (entry 9). The reaction of diphenylketene went smoothly, but only 78% ee was achieved (entry 10). The symmetric cyclic ketene, cycloheptylideneemethanone, which worked well in Fu's ketene-aldehyde cycloaddition, gave the product in only 63% yield with very low enantioselectivity (entry 11). And the reaction of **2a** and benzil (PhCOCOPh) did not occur under the current reaction conditions (entry 12).

One possible catalytic cycle for this NHC-catalyzed reaction is depicted in Figure 1. The N-heterocyclic carbene attacks the α-carbon of the ketene to give a triazolium enolate **9**. The nucleophilic addition of enolate **9** to aldehyde furnishes triazolium aldolate **10**, which collapses to afford the desired β-lactone **4** and regenerate NHC catalyst.

In conclusion, the N-heterocyclic carbene **5b** was demonstrated as an efficient catalyst for the formal cycloaddition of

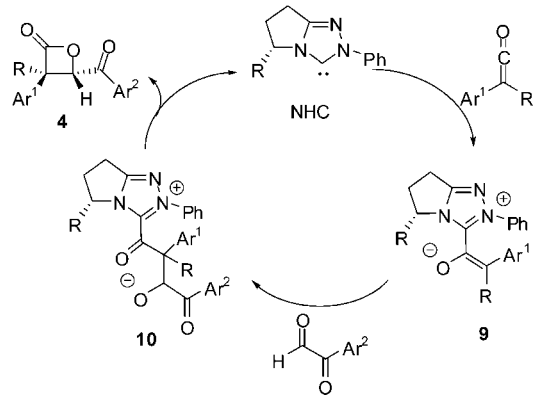


FIGURE 1. Proposed catalytic cycle.

alkyl(aryl)ketenes with 2-oxoaldehydes to give the corresponding β-lactones with α-quaternary-β-tertiary stereocenters in good yields with good diasteroselectivities and excellent enantioselectivities. Further exploration of NHC-catalyzed reaction of ketenes is underway in our laboratory.

Experiment Section

General Procedure for Asymmetric Synthesis of β-Lactones. To an oven-dried 50 mL reaction tube containing a stir bar were added triazolium salts **5b′** (70 mg, 0.12 mmol), anhydrous Cs_2CO_3 (32 mg, 0.1 mmol), and THF (4 mL). The reaction mixture was stirred for 1 h at room temperature. Ketene (1.5 mmol) was then added via a syringe followed by addition of 2-oxoaldehyde (1.0 mmol), and the reaction mixture was stirred overnight. The mixture was then filtered through a pad of silica gel and washed with petroleum ether/ethyl acetate (10:1). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to give the desired product as a white solid.

Lactone **4a** (Table 2, entry 1). Yield: 266 mg (85%); $R_f = 0.61$ (petroleum ether/ethyl acetate = 10:1); white solid, mp 125−126 °C; $[\alpha]^{25}_D$ −20.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.5$ Hz, 2H), 7.74−7.58(m, 2H), 7.55−7.45 (m, 2H), 7.45−7.38 (m, 1H), 7.38−7.29 (m, 2H), 5.93 (s, 1H), 2.49−2.27 (m, 1H), 2.26−2.06 (m, 1H), 0.84 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 170.1, 136.2, 134.1, 133.2, 132.4, 131.0, 129.7, 129.4, 128.8, 128.7, 127.0, 77.7, 69.6, 23.5, 9.1; IR (KBr) υ 1830, 1696, 1597, 1449, 1231, 1120, 914, 754, 697; EIMS *m*/*z* 314 (M^+, 1.28), 270 ($M^+ - CO_2$, 10.36), 235 ($M^+ - CO_2 - {}^{35}Cl$, 65.85), 105 ($PhCO^+$, 100); HRMS-EI (*m*/*z*) [M^+] calcd for $C_{18}H_{15}ClO_3$, 314.0710; found 314.0713. HPLC analysis: 97% ee [Daicel CHIRALPAK AS-H column; 20 °C; 1.0 mL/min; solvent system = 2-propanol/hexane, 10:90; retention times = 11.5 min (major), 15.4 min (minor)].

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Supporting Information Available: Experimental procedures, compound characteriations, and crystal structure data of lactone **4b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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