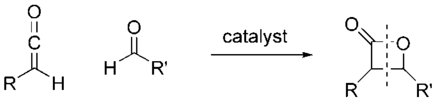
Lactone Synthesis

Asymmetric Synthesis of Highly Substituted β-Lactones by Nucleophile-Catalyzed [2+2] Cycloadditions of Disubstituted Ketenes with Aldehydes[**]

*Jonathan E. Wilson and Gregory C. Fu**

The development of effective methods for the asymmetric synthesis of β-lactones is an important challenge for a variety of reasons.[1] Numerous biologically active β-lactone-containing natural and unnatural products have been described, including Xenical (tetrahydrolipstatin), an anti-obesity drug developed by Roche.[2,3] Furthermore, β-lactones serve as useful intermediates in an array of fields, including materials science and synthetic organic chemistry.[1,4] The strain of the four-membered lactone provides an opportunity for a range of functionalizations; for example, nucleophiles can react either at the carbonyl group through an addition–elimination sequence or at a C–O single bond through an S_N2 process. Thus, a number of recent total syntheses, such as those of (−)-laulimalide,[5] (−)-malyngolide,[6] and trapoxin B,[7] have exploited enantiopure β-lactones as intermediates.

One attractive route to β-lactones is the overall [2+2] cycloaddition of a ketene with an aldehyde [Eq. (1)]. Chiral nucleophiles and chiral Lewis acids have both been shown to catalyze this process, sometimes with outstanding enantioselectivity (the postulated mechanism for the nucleophile-catalyzed cycloaddition is illustrated in Scheme 1).[8–11] To date, all reports of asymmetric catalysis of this transformation have described reactions of ketene itself ($H_2C{=}C{=}O$) or of *mono*substituted ketenes. Expanding the scope of such processes to include *di*substituted ketenes would furnish access to α,α-disubstituted β-lactones, an important class of synthetic targets.[12]



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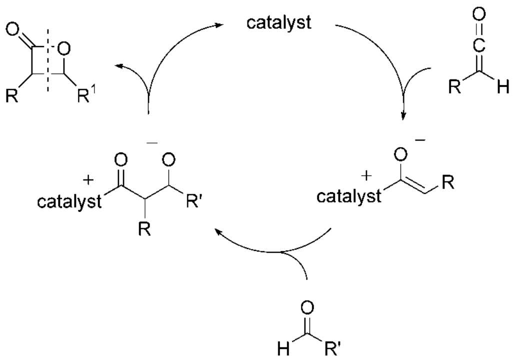
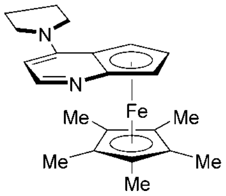


Scheme 1. Proposed pathway for the nucleophile-catalyzed enantioselective synthesis of β-lactones from ketenes and aldehydes.

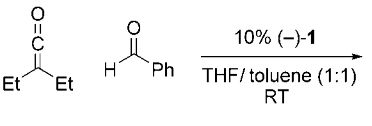
We have been exploring the utility of planar-chiral DMAP and PPY derivatives (for example, **1**) as catalysts for a range of transformations,[13] including an asymmetric Staudinger synthesis of β-lactams that likely proceeds by a pathway analogous to that depicted in Scheme 1 (DMAP = 4-(dimethylamino)pyridine, PPY = 4-pyrrolidin-1-ylpyridine).[14]



(−)-**1**

We were intrigued by the possibility that these nucleophilic catalysts might also be useful for β-lactone synthesis. This sort of an "extension" from reactions of imines to reactions of aldehydes is not as straightforward as may appear; for example, in the case of cinchona alkaloid-based catalysts, an excellent method for enantioselective β-lactam synthesis from monosubstituted ketenes was reported several years ago,[15] whereas general conditions for β-lactone synthesis from monosubstituted ketenes, which require a Lewis acid co-catalyst, have only been developed very recently.[16] In this Communication, we demonstrate that PPY derivative **1** serves as an effective catalyst for [2+2] cycloadditions of *di*substituted ketenes with aldehydes to furnish the first catalytic asymmetric route to α,α-disubstituted β-lactones.

In our earlier study, we established that **1** catalyzes a Staudinger-type cycloaddition of ketenes with imines to efficiently afford β-lactams with good enantioselectivity (76–98% yield; 81–98% *ee*).[14] However, when we apply these conditions to the corresponding reaction of ketenes with aldehydes, we obtain essentially none of the desired β-lactone [Eq. (2)].



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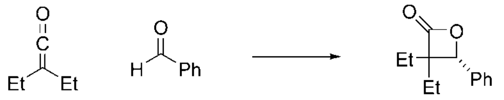
Interestingly, by lowering the reaction temperature, we can generate the targeted [2+2] cycloaddition product in high yield, and, equally significantly, in high enantiomeric excess (91 % yield, 89 % *ee*; Table 1, entry 1). Furthermore, the two-solvent system that we employed for the synthesis of β-lactams is unnecessary—the formation of β-lactones proceeds in very good yield and *ee* in THF alone (entry 2). It is important to note that the alkaloid-based methods that have proved useful for catalytic asymmetric reactions of *mono*-substituted ketenes are not effective for the illustrated cycloaddition of a *di*substituted ketene (entries 3[10b] and 4[10d]).

Table 1: Catalytic asymmetric cycloaddition of diethylketene with benzaldehyde.

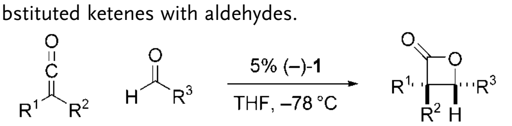


Entry	Catalyst	Conditions	Yield [%][a]	*ee* [%][a]
1	5 % (−)-**1**	THF/toluene (1:1), −78 °C	91	89
2	5 % (−)-**1**	THF, −78 °C	92	91
3	5 % quinidine	THF/toluene (1:1), −78 °C→RT	< 5	–
4[b]	10 % *O*-TMS-quinidine, 2 equiv $LiClO_4$	THF/CH_2Cl_2 (1:1), −78 °C→RT	21	< 2

[a] Average of two runs. [b] Because the product β-lactone could not be separated from a side product, the β-lactone was reduced to a 1,3-diol with diisobutylaluminum hydride (DIBAL-H). TMS = trimethylsilyl.

Our optimized conditions (Table 1, entry 2) are applicable to a range of [2+2] cycloadditions of disubstituted ketenes with aldehydes (Table 2). Thus, symmetrical ketenes, both acyclic and cyclic, couple with aldehydes with good enantioselectivity (entries 1–7). Cycloadditions of unsymmetrical disubstituted ketenes generate β-lactones that bear two contiguous stereocenters, one quaternary and one tertiary;[17] we have determined that planar-chiral catalyst **1** preferentially furnishes the *cis* diastereomer (ca. 4.5:1 selectivity) with very good *ee* (ca. 90 %; entries 8 and 9).[18]

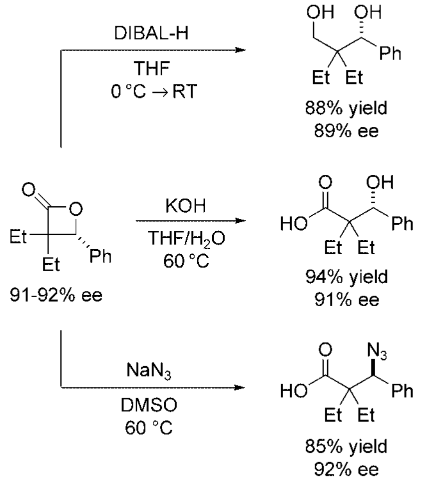
Table 2: Catalytic asymmetric synthesis of β-lactones by cycloadditions of disubstituted ketenes with aldehydes.



Entry	R^1	R^2	R^3	*ee* [%][a]	Yield [%][a]
1	Et	Et	Ph	91	92
2	Et	Et	2-naphthyl	89	77
3	Et	Et	4-$(CF_3)C_6H_4$	80	74
4	Et	Et	4-$(MeCO)C_6H_4$	81	76
5	Et	Et	4-MeC_6H_4	89	67
6[b]	Me	Me	Ph	76	68
7	-$(CH_2)_6$-		Ph	82	71
8[c]	*i*Pr	Me	Ph	91	48
9[c]	cyclopentyl	Me	Ph	88	53

[a] Average of two runs. [b] 7 % (−)-**1** was used. [c] *cis*:*trans* selectivity = 4.2–4.6:1. The *ee* value is for the *cis* diastereomer, and the yield is for both diastereomers.

We have established that these sterically demanding α,α-disubstituted β-lactones can be derivatized through reactions with nucleophiles (Scheme 2). Reagents such as DIBAL-H and hydroxide add to the carbonyl group to furnish a 1,3-diol and a β-hydroxyacid, respectively. Sodium azide, on the other hand, reacts through an S_N2 process to generate a β-azidoacid.[19,20] These functionalizations proceed in good to excellent yield with essentially no erosion in enantiomeric excess.[21]



Scheme 2. Derivatization of α,α-disubstituted β-lactones.

In conclusion, we have established for the first time that a chiral PPY derivative (**1**) can serve as an efficient catalyst for the asymmetric synthesis of β-lactones; this is the only catalyst reported to date that is effective for enantioselective cycloadditions of disubstituted ketenes, which generate α,α-disubstituted β-lactones. Furthermore, we have shown that these β-lactones, in addition to being useful structures in their own right, can be transformed into other important families of enantioenriched compounds. Additional studies of catalytic asymmetric reactions of ketenes are underway.

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[18] Notes: a) Under our standard conditions (Table 2), aryl alkyl ketenes, monosubstituted ketenes, very electron-rich aldehydes, and non-aromatic aldehydes are not suitable substrates. b) At the end of a reaction, we can typically recover about 80% of catalyst **1**.

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