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Phosphine-Catalyzed Asymmetric Synthesis of β-Lactones from Arylketoketenes and Aromatic Aldehydes

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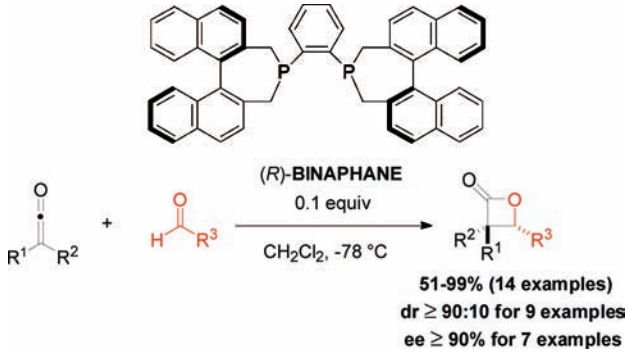
ABSTRACT



In this paper, the development of a chiral phosphine-catalyzed formal [2 + 2] cycloaddition of aldehydes and ketoketenes that provides access to a variety of highly substituted β-lactones (14 examples) is reported. The BINAPHANE catalytic system displays excellent enantioselectivity (seven examples with ee ≥90%) and high diastereoselectivity favoring formation of the *trans*-diastereomer (nine examples with dr ≥90:10).

β-Lactones are important molecules which are found as integral structural features of many pharmacologically active molecules and, in addition, have been extensively used as intermediates in complex molecule synthesis.[1,2] Both chiral Lewis acid and chiral nucleophile catalyzed approaches to enantioenriched β-lactones have been investigated.[3] The most versatile methodologies providing access to enantioenriched β-lactones rely on the use of alkaloid nucleophiles to catalyze the formal [2 + 2] cycloaddition of ketenes and aldehydes.[3] The seminal work of Wynberg's group in the early 1980s showed that cinchona alkaloid catalysts (quinine and quinidine) could catalyze the formal [2 + 2] cycloaddition of ketene with chloral to afford a β-lactone in highly enantioselective fashion.[4] Subsequent advances were made by the groups of Romo, Nelson, and Calter to extend the substrate

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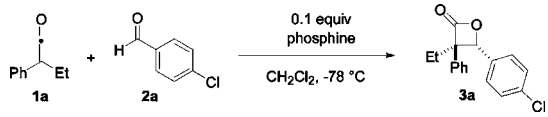
scope of this reaction to include unactivated aldehydes.[5−7] The expeditious use of mild Lewis acids, such as $LiClO_4$ or $Sc(OTf)_3$, in combination with nucleophilic catalysis was particularly noteworthy.[6,7] However, all of these systems have been limited with respect to the ketene substrate tolerated; only ketene or simple monosubstituted ketenes can be used as substrates with the alkaloid catalytic systems, presumably due to their attenuated nucleophilicity. Fu's group showed that planar chiral ferrocenylamine catalysts could catalyze the reaction of dialkylketenes with aromatic aldehydes in high enantioselectivity, but with moderate diastereoselectivity (dr up to 4.6:1). Moreover, their system was not successful with aliphatic aldehydes or with alkylarylketenes.[8] Recently, Ye's group showed that the reaction of alkylarylketenes with highly electrophilic 2-oxoaldehydes could be catalyzed by a chiral N-heterocyclic carbene catalyst.[9] However, they found that less reactive aldehydes such as aromatic aldehydes were not tolerated as substrates by their weakly nucleophilic catalytic system.

With the broad goal of applying highly substituted β-lactones, possessing vicinal quaternary and tertiary stereogenic centers, to complex molecule synthesis, we investigated phosphines as nucleophilic catalysts for the formal [2 + 2] cycloaddition of ketoketenes and aldehydes. We envisaged that a phosphine catalytic system would supersede these previously reported systems due to the enhanced polarizability of the phosphorus atom relative to that of the nitrogen atom in amines.[10] The reaction of ethylphenylketene with 4-chlorobenzaldehyde was used as the test reaction for methodology optimization (Table 1).

Table 1. Catalyst Screening for the Formal [2 + 2] Cycloaddition of Ketoketenes and Aldehydes



entry	catalyst	addition time of **1a** (h)	% convn[a] (% yield)	dr[b]	% ee[c]
1	PBu_3	direct	20	90:10	
2	PBu_3	4	91	95:5	
3	PBu_3 + LiI (0.3 equiv)	direct	>99	60:40	
4	Duanphos	4	0		
5	Josiphos	4	(19)	56:44	n.d.
6	(*R*,*R*)-**4**	4	6	71:29	n.d.
7	(*R*)-**5**	4	(63)	92:8	32
8	BINAPHANE	4	(94)	93:7	64

[a] % convn = % conversion to **3a**; % yield is isolated yield for **3a**. [b] Diastereomeric ratio (dr) determined by HPLC or ^{1}H NMR analysis. [c] % ee determined by chiral HPLC analysis.

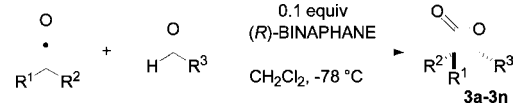
We carried out our initial optimization of the reaction with PBu_3 as the catalyst as we had found it to be a successful achiral catalyst for the dimerization of a variety of ketoketenes.[11] It was found necessary to add the ketoketene solution via syringe pump over 4 h to the aldehyde/phosphine solution in order to minimize ketoketene dimerization (entry 1 vs entry 2).[11] Addition of a Lewis acid (LiI) led to much lower diastereoselectivity, presumably due to competing transition states, and was not investigated further (entry 3).[6,7]

With the aim of rendering the reaction asymmetric we then examined a number of chiral catalysts, including those that we had previously found promising in catalyzing enantioselective ketoketene dimerization (BINAPHANE) and those that had shown success in other organocatalytic settings.[11,12] Axially chiral (*R*)-BINAPHANE was found to be the optimal catalyst with respect to reactivity, diastereoselectivity, and enantioselectivity (Table 1, entry 8).[13]

The scope of the BINAPHANE-catalyzed methodology with respect to ketoketene and aldehyde structure was then explored (Table 2). Reactions proceeded with 70−99% conversion after 12−16 h, but crude products typically contained 5−20% unreacted aldehyde. Therefore, most isolated yields were determined following ring-opening of crude β-lactones **3** with aqueous KOH to afford the corresponding β-hydroxycarboxylic acids **4** as analytically pure compounds (see the Supporting Information for procedures).

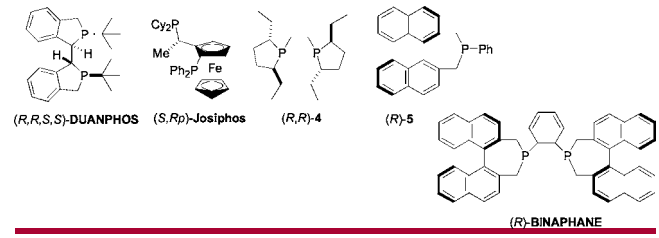
A variety of ketoketene aryl, including indolyl (entry 4−6) and alkyl substituents (entry 3 vs entry 9 vs entry 10), were tolerated, while even the sterically hindered

Table 2. Scope of Phosphine-Catalyzed Formal [2 + 2] Cycloaddition



entry	R^1	R^2	R^3	% yield[a]	dr[b]	% ee[c]
1	Ph	Me	Ph	87	96:4	79
2	Ph	Me	4-ClPh	65	95:5	90
3	Ph	Me	4-NO_2Ph	63	94:6	92
4	indolyl[d]	Et	4-ClPh	75	83:17	>99
5	indolyl	Et	CH_2CH_2Ph	61	>99:1	97
6	indolyl	Et	$(CH_2)_3CH_3$	59	>99:1	93
7	Ph	Et	2-ClPh	>99[e]	75:25	n.d.
8	Ph	Et	4-ClPh	94[e]	93:7	64
9	Ph	Et	4-NO_2Ph	51	80:20	87
10	Ph	*n*-Bu	4-NO_2Ph	99	53:47	61/96
11	2-tolyl	Me	4-NO_2Ph	72	96:4	54
12	4-tolyl	Me	4-ClPh	72	92:8	84
13	4-tolyl	Me	4-NO_2Ph	55	90:10	85
14	Ph	Ph	4-NO_2Ph	62[e]		96

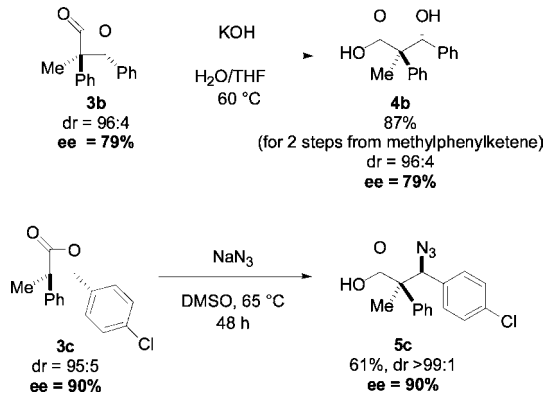
[a] Isolated yield (%) for β-hydroxy acid **4** derived from β-lactone **3** unless stated otherwise. [b] Diastereomeric ratio (dr) determined by HPLC or ^{1}H NMR analysis. [c] % ee determined by chiral HPLC analysis for major diastereomer. [d] Indolyl = *N*-Me-3-indolyl. [e] Isolated yield (%) for β-lactone **3**.



diphenylketene proved a successful substrate (entry 14).[14] In general, aromatic aldehydes, particularly those possessing electron-withdrawing aromatic substituents (NO_2 or Cl), gave very good levels of diastereoselectivity and enantioselectivity (e.g., entries 2, 3, 12, and 13). Less activated aromatic aldehydes such as benzaldehyde also functioned well with good diastereoselectivity and with slightly lower enantioselectivity being obtained (entry 1). It was especially noteworthy that the method could be extended to some unactivated aliphatic aldehydes (entries 5 and 6) with excellent levels of asymmetric induction (>90%) being displayed.[6,15] Poor diastereoselectivity was observed in some cases (Table 2, entries 7 and 10), and this is presumably due to competing reaction mechanisms (see Scheme 2, mechanism A vs mechanism B).

The potential synthetic utility of highly substituted β-lactones **3** can be estimated from the relative ease with which they may be converted to useful synthons such as β-hydroxy carboxylic acids **4** and β-azido carboxylic acids **5** (Scheme 1).[16] Although **3b** was obtained in lower ee than many

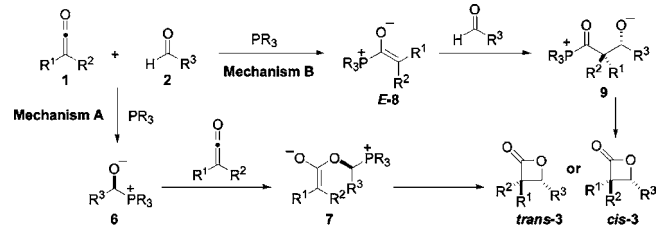
Scheme 1. Ring-Opening Reactions of β-Lactones **3**



examples in Table 2, it served as an effective representative example to evaluate retention of chirality during KOH-promoted hydrolysis. Efficient transfer of chirality was noted both for the conversion of **3b** (79% ee) to β-hydroxy carboxylic acid **4b** (79% ee) and for the conversion of **3c** (90% ee) to β-azido carboxylic acid **5c** (90% ee). No erosion of diastereomeric purity was detected in either case.

We speculate that the mechanism for formation of *trans*-**3** involves initial attack of BINAPHANE on aldehyde **2** to give phosphonium alkoxide **6** (Scheme 2).[17] Indeed, there is precedence for such a mode of addition in the work of Fu's group on the synthesis of *trans*-β-lactams from ketoketenes and *N*-triflyl imines. They provided both ^{1}H NMR and X-ray crystallographic evidence that the nucleophilic catalyst, a chiral 4-(pyrrolidino)pyridine derivative, adds first to the *N*-triflylimine rather than to the ketoketene.[18] In the BI-

Scheme 2. Postulated Mechanisms A and B for Phosphine-Catalyzed Formal [2 + 2] Cycloaddition of Ketoketenes and Aldehydes



$PR_3 = PBu_3$ or BINAPHANE
$R^1 > R^2$

NAPHANE system, phosphonium alkoxide **6** would add to another molecule of ketoketene **1** to generate enolate **7**. Intramolecular S_N2 (4-*exo*-*tet*) would provide *trans*-**3** as the major product.

Although the more commonly encountered mechanism B cannot be ruled out at this point, tentative support for mechanism A was derived from a number of observations. The sense of enantioselectivity in the (*R*)-BINAPHANE-catalyzed dimerization of methylphenylketene (31% ee, (*S*)-enantiomer = major, see the Supporting Information for procedure), a process that is presumed to involve phospho-

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(13) The relative stereochemistry of β-lactones **3** was determined to be *trans* through X-ray crystallographic analysis of (±)-**3d**. See the Supporting Information for further details.

(14) The absolute configuration of **3n** (entry 14, Table 2) was determined to be (*R*) through X-ray crystallographic analysis (see the Supporting Information for further details). The absolute configuration of β-lactones **3a**−**m** was assigned to be (*R*,*R*) by analogy.

(15) Aliphatic aldehydes possessing α-branching, such as isobutyraldehyde, were also investigated but gave lower yields (<40%).

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nium enolate intermediate *E*-**8**, differed from that of the (*R*)-BINAPHANE-catalyzed reaction of methylphenylketene and 4-NO_2PhCHO (92% ee, (*R*,*R*)-enantiomer = major).[11,14,17] While the large difference in the degree of enantioselectivity could be interpreted in terms of different transition-state energies for each electrophile (one having a later transition state than the other), the different sense of enantioselectivity is less easily explained by a mechanism involving enolate *E*-**8** in both reactions. Equilibration of enolate *E*-**8** to the *Z*-isomer would presumably be required to provide a different configuration at the quaternary stereocenter of **3** to that of methylphenylketene dimer **10**. In nucleophile-catalyzed reactions of ketenes, such a process has only been proposed to occur under very specialized conditions (using an anionic imidazoline catalyst at 0 °C) and is unlikely to occur under the present reaction conditions (neutral catalyst at −78 °C).[19] Furthermore, subjecting a stoichiometric amount of phosphonium enolate **8**, derived from diphenylketene and PBu_3, to reaction with 4-NO_2PhCHO resulted in no β-lactone (**3n**) being formed. This was in contrast to the result of the BINAPHANE-catalyzed reaction (Table 2, entry 14). Indeed, if the reaction was to involve a phosphonium enolate intermediate **8**, one would expect a higher level of enantioselectivity to be observed in reactions with electronically less reactive aldehydes due to the involvement of a later transition state (a trend that was observed in Fu's studies).[8] This is not the case with the BINAPHANE system as 4-NO_2PhCHO gives superior enantioselectivity to 4-ClPhCHO (Table 2, entries 8 vs 9) and PhCHO (Table 2, entries 1 vs 3). It is also interesting to note that the analogous ferrocenylamine system of Fu catalyzes the formal [2 + 2] cycloaddition of dialkylketenes and aromatic aldehydes to give *cis*-β-lactones, via a postulated ammonium enolate intermediate.[8] Mechanistic investigations will be carried out to clarify which of the two mechanisms (A or B) is operative in the BINAPHANE system.[20]

In summary, we have developed a versatile chiral phosphine-catalyzed formal [2 + 2] cycloaddition of aldehydes and ketoketenes that provides access to highly substituted β-lactones with excellent enantioselectivity (≥90% ee for seven examples) and good diastereoselectivity (≥90:10 for nine examples). Future studies will focus on elucidating the mechanism, the substrate scope with respect to chiral aldehydes, and the mode of enantioselectivity of this reaction.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic files (CIF). This information is available free of charge via the Internet at http://pubs.acs.org.

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(20) ^{31}P NMR monitoring of the PBu_3-catalyzed reaction of 4-NO_2PhCHO and diphenylketene was inconclusive, with signals observed at 13.4, 28.2, and 34.2 ppm .