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Phosphine-catalyzed synthesis of β -lactones from ketenes and chiral β -oxyaldehydes

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ABSTRACT

In this letter we describe a catalytic procedure for the diastereoselective synthesis of β -lactones bearing up to three stereogenic centers, from disubstituted ketenes and chiral β -oxyaldehydes. Tri-*n*-butylphosphine was determined to be the best catalyst with yields of up to 95% and moderate to good diastereoselectivity (dr up to 4:1) obtained in the formation of highly substituted β -lactones.

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Aldol reactions and related surrogate aldol reactions (e.g. β -lactone forming reactions) are one of the most widely used methods for C-C bond construction in the synthesis of complex molecules.^{1,2} The diastereoselective assembly of aldol architecture through the reaction of enolates with chiral β -oxyaldehydes is a route of great potential for complex molecule synthesis. Evans' group has carried out extensive studies to unravel mechanistic details of Lewis acid-mediated reactions of metal enolates with chiral β -oxy- and α,β -oxysubstituted aldehydes.^{3,4} A number of other groups have also reported success utilizing a Lewis acid-mediated approach to control diastereoselectivity in aldol reactions of chiral β -oxyaldehydes.⁵⁻⁸ The most relevant studies include those by Romo's group and Zhang's group preparing statins (Panclidin D and tetrahydrolipstatin) through an approach involving a Lewis acid-catalyzed addition of a silylketene acetal to a chiral β -oxyaldehyde.^{5,7} Super-stoichiometric amounts (1.2-2.0 equivalents) of the Lewis acid (ZnCl_2) were required to catalyze the reaction. Indeed, in all of the studies mentioned involving Mukaiyama aldol reactions, at least one equivalent of a Lewis acid was needed to promote the reaction. However there have been no reports of disubstituted ketenes acting as pronucleophiles in the diastereoselective synthesis of β -lactones from chiral β -oxyaldehydes.^{9,10} Moreover, catalytic approaches to aldol reactions (and surrogate aldol reactions) of chiral β -oxyaldehydes are extremely rare, and the development of catalytic aldol/surrogate aldol-type processes is a research area of great interest in organic synthesis.^{9,11,12}

In recent years, we determined that an axially chiral phosphine, known as binaphane, could catalyze the formal [2 + 2] cycloaddition of alkylarylketenes with aromatic aldehydes and some aliphatic aldehydes to give β -lactones.¹³⁻¹⁶ Earlier in 2015, we reported that the PBu_3 -catalyzed reaction of disubstituted ketenes with chiral α -oxyaldehydes favored formation of the *anti*-diastereomer of β -lactones with moderate to excellent levels of diastereocontrol (dr up to 32:1).¹⁵ We anticipated that the reaction of chiral aldehydes possessing an β -oxy substituent would also provide a useful route to complex molecules (for example, to statin drug analogues).^{5,7}

In this letter we report that a catalytic amount of a trialkylphosphine facilitates the formation of β -lactones bearing up to three stereogenic centers, from disubstituted ketenes and chiral oxyaldehydes possessing β -stereogenic centers, with moderate to good levels of diastereoselectivity (dr up to 4:1).

We began our study by evaluating a variety of phosphine nucleophilic catalysts for success in promoting the formal [2 + 2] cycloaddition of methylphenylketene **1** with chiral β -oxyaldehyde **2a** (Table 1). (*R*)-Binaphane had previously demonstrated high reactivity in catalyzing the reaction of disubstituted ketenes with aromatic and some aliphatic aldehydes.^{13,14} However it proved to be completely ineffective when encountering chiral aldehyde **2a** as a substrate (Table 1, entries 1 and 2). We surmise that the low reactivity of the β -oxy substituted aldehyde coupled with the sterically bulky nature of binaphane and related phosphine catalysts is responsible for the low conversions observed. This was further borne out by the fact that tricyclohexylphosphine, a phosphine with a large cone angle, proved totally ineffective (Table 1, entry 7).¹⁷ Following

extensive exploration of achiral trialkylphosphines, it was found that tri-*n*-butylphosphine was the optimal catalyst, in terms of effecting both good conversion and promising diastereoselectivity (dr = 3:1) (Table 1, entry 9).

Table 1. Optimization of reaction of chiral β -oxaldehydes.

Entry	PR ₃	% conv ^a	dr ^b
1	(<i>R</i>)-BINAPHANE	0	
2	(<i>R</i>)-BINAPHANE/LiI	8	2:1
3	(<i>R</i>)- <i>t</i> -Bu-binepine	26	1:1
4	(<i>R</i>)-Ph-binepine	0	
5	(<i>R</i>)-Et-binepine	0	
6	dppb	8	1:1
7	P(<i>c</i> -hexyl) ₃	0	
8	PMe ₃	>99	1:1
9	PBu ₃	90	3:1
10	PBu ₃ /LiI	18	1:1
11	PBu ₃ /LiClO ₄	<10	1:1
12	PBu ₃ /Me ₂ AlCl	<10	1:1
13	PBu ₃ /ZnBr ₂	<10	1:1

^a % conv = conversion of aldehyde to product as determined by GC-MS analysis of crudes. ^b dr = diastereomeric ratio represents ratio of major diastereomer to minor diastereomer(s); determined by GC-MS or ¹H NMR analysis of crudes.

The minor diastereomer of **3a** was determined to be the *anti,anti*-isomer by X-ray crystal structure analysis of its 3,5-dinitrobenzoate derivative (**4a**). NOESY experiments performed on both diastereomers of **4a** (derived from **3a**) showed that the major diastereomer of **3a** is the *anti,syn*-isomer (see supplementary information for spectra). The formation of the *anti,syn*-diastereomer as the major diastereomer was rationalized through the model depicted in Figure 1.

The *anti,syn*-diastereoselectivity (1,3-*syn* selectivity) observed in our reaction is consistent with a transition state (TS2) in which the nucleophile (phosphonium enolate **A** or **B**) approaches the aldehyde along a trajectory *anti* to the largest α -substituent (alkyl group), with dipoles associated with the C=O and C-O(PG) minimized (Figure 1).^{4,6} The relatively small steric demand of the R = CH₂CH₂Ph group ensures that gauche interaction with the H atom of the aldehyde group is not overly severe in TS2. We speculate that the preference for *anti*-stereochemistry across the β -lactone ring may be due to an anti-periplanar arrangement in the transition state involving enolate **A/B** and the aldehyde or, alternatively, a 7-membered cyclic transition state in which the phosphonium ion of **B** activates the aldehyde carbonyl to nucleophilic attack by the enolate of **B**.^{14,18}

Figure 1. Rationale of diastereoselectivity in reaction of chiral β -oxaldehydes.

We then proceeded to investigate the scope of the reaction by evaluating a range of alkylarylketenes and dialkylketenes in reaction with chiral β -oxysubstituted aldehydes **2a–2c** (Table 2).

Table 2. Substrate scope involving chiral β -oxaldehydes.^{19,20}

Entry	RCHO	R ¹	R ²	% Yield ^a	dr ^b	Lactone
1	2a	Ph	Me	61	3:1	3a
2	<i>ent</i> - 2a ^c	Ph	Me	59	3:1	3b
3	2a	Ph	Et	95	1.2:1	3c
4	2a	Ph	<i>n</i> -Bu	57	1.1:1	3d
5	2a	<i>c</i> -Hex	Me	79	3:1	3e
6	2a	<i>i</i> -Pr	Me	56	3:1	3f
7	2a	Indolyl	Et	48	4:1	3g
8	2a	Me	Me	45	2:1	3h
9	2b	Ph	Me	47	4:1	3i
10 ^d	2c	Ph	Me	81	1:1	3j
11 ^d	<i>ent</i> - 2c ^c	Ph	Me	63	1:1	3k

^a Isolated yield (%) for all diastereomers. ^b dr = diastereomeric ratio represents ratio of major diastereomer to minor diastereomer(s); determined by GC-MS or ¹H NMR analysis of crudes. ^c *ent*-**2a** = enantiomer of **2a**; *ent*-**2c** = enantiomer of **2c**. ^d PMe₃ (10 mol%) was used as catalyst.

The chiral β -oxysubstituted aldehydes gave moderate diastereoselectivity in most cases (typically dr 3:1 to 4:1), with best results being obtained with a PMB group on the β -oxygen atom (entry 9, dr 4:1). Best levels of diastereoselectivity were observed in the reactions of unsymmetrical ketenes where there was a significant difference in the steric size of the substituents (e.g., methylphenylketene). In cases where there was less steric differentiation between ketene substituents, substantially lower diastereoselectivity was observed. For example, both ethylphenylketene and *n*-butylphenylketene in reaction with **2a** gave a dr of ca. 1:1 (Table 2, entries 3 and 4). Symmetrical ketenes, such as dimethylketene, also gave lower diastereoselectivity (dr = 2:1, entry 8).

Occasionally it was necessary to use PMe_3 rather than PBu_3 due to low conversions (ca. 10% conv) obtained with the first choice catalyst (Table 2, entries 10 and 11). As a result, poor diastereoselectivity was observed for reactions of chiral aldehyde **2c**, a result in keeping with our earlier observations regarding diastereoselectivity obtained in the PMe_3 -catalyzed reaction of aldehyde **2a** (Table 1, entry 8).

^{31}P NMR monitoring at -78°C of the formation of **3a** from **2a**, revealed signals at 13.8 ppm, 14.9 ppm, and 32–34 ppm. All of these signals are found in a range characteristic of tetravalent phosphonium species.^{14,21,22} Therefore it is tempting to infer that the reaction involves ketene-derived phosphonium enolate intermediates (e.g., **A** or **B**, Figure 1). However, further mechanistic investigations (experimental and computational) will have to be carried out to determine whether phosphonium enolates are legitimate intermediates in the catalytic cycle.

In conclusion, a phosphine-catalyzed methodology for the diastereoselective synthesis of β -lactones bearing up to three stereogenic centers from disubstituted ketenes and chiral β -oxyaldehydes has been developed. β -Lactones were obtained in moderate to excellent yields (up to 95%) and with moderate to good diastereoselectivity (dr up to 4:1). Future work will involve the design and evaluation of chiral phosphine catalysts with appropriate reactivity to enable studies of double diastereoselection with chiral β -oxyaldehydes.

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- Experimental procedure for preparation of **3a**: To a stirring solution of (S)-3-(tert-butyldimethylsilyloxy)-5-phenylpentanal (69 mg, 0.24 mmol, 1 equiv) and PBu_3 (5 mg, 0.025 mmol, 0.1 equiv) in CH_2Cl_2 (0.2 mL) at -78°C under nitrogen atmosphere, was added a solution of methylphenylketene (32 mg, 0.24 mmol, 1 equiv) in CH_2Cl_2 (0.4 mL) over a period of 4 h using a syringe pump. The reaction was stirred at -78°C for another 4 h. The reaction was then allowed to warm up to room temperature gradually over 12 h in the cooling bath (total reaction time = 20 h). The crude solution was passed through a plug column (Iatrobeds, 2.5×3.0 cm, 6 g) [ca. 50 $\times$ estimated weight of product mixture]. The plug column was eluted with a 10% EtOAc/hexane solvent system (250 mL), and the solvent was removed under vacuum to furnish the desired β -lactone **3a** as a slightly yellowish gel-like solid (61 mg, 61%), dr = 3:1 (by ^1H NMR).
- Characterization data for **3a**: IR (CH_2Cl_2): 3027, 2953, 2929, 2856, 1824, 1496, 1471, 1455, 1255, 1155, 1094, 1067, 878, 835, 775, 749, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , TMS) for the major diastereomer: δ 7.46–7.37 (m, 3H), 7.37–7.27 (m, 4H), 7.26–7.19 (m, 3H), 5.01 (dd, J = 8.9, 3.2 Hz, 1H), 4.11–3.99 (m, 1H), 2.82–2.64 (m, 2H), 2.21–2.09 (m, 2H), 1.98–1.86 (m, 2H), 1.63 (s, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) for the major diastereomer: δ 173.4, 142.1, 140.3, 129.3, 128.7, 128.6, 127.9, 126.1, 125.6, 79.6, 69.3, 62.0, 38.6, 37.7, 32.3, 26.1, 19.7, 18.3, -4.2, -4.2; (M + H) $^+$ HRMS m/z calcd for $(\text{C}_{26}\text{H}_{37}\text{O}_3\text{Si})^+$: 425.2512; Found: 425.2512.
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