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Phosphine-Catalyzed Diastereoselective Synthesis of β-Lactones from Disubstituted Ketenes and α-Chiral Oxyaldehydes

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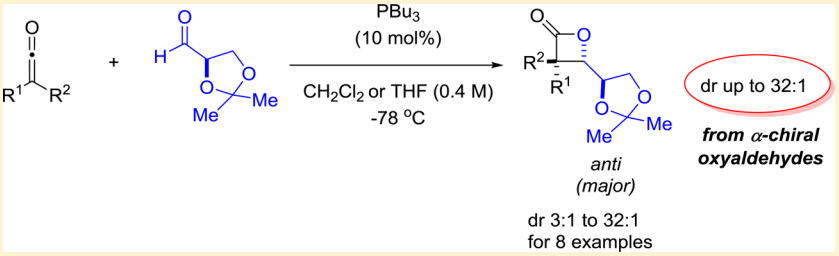
Supporting Information



ABSTRACT: In this article we describe a catalytic procedure for the diastereoselective synthesis of β-lactones bearing two stereogenic centers, from disubstituted ketenes and α-chiral oxyaldehydes. Tri-*n*-butylphosphine was found to be the optimal catalyst in terms of effecting both good yield and diastereoselectivity (dr from 3:1 to 32:1 for 8 examples) in β-lactone formation. The major isomer of the β-lactone products was determined to be the *anti*-diastereomer, and its formation was rationalized by a polar Felkin−Anh model. Involvement of phosphonium enolate intermediates in the reaction mechanism was indicated through reaction monitoring by ^{31}P NMR spectroscopy. The utility of the methodology is demonstrated by a short synthesis of a (+)-peloruside A synthon.

INTRODUCTION

Aldol reactions and surrogate aldol reactions have been used widely in complex molecule synthesis.[1,2] Evans and co-workers have carried out extensive studies developing chiral auxiliary-controlled diastereoselective aldol reactions as well as aldol reactions controlled by double diastereoselection.[2] Nelson's group has previously shown that cinchona alkaloid derivatives can catalyze the double diastereoselective synthesis of β-lactones from α-chiral aldehydes and in situ generated methylketene.[3] However, alkaloid catalysts are generally too unreactive to engage disubstituted ketenes, and so β-lactones bearing quaternary (stereogenic or otherwise) centers cannot be accessed using Nelson's methodology.[3−6] Mahrwald's group reported that histidine could catalyze the aldol reaction of α-chiral aldehydes (4 examples in all).[7] Unfortunately, only moderate diastereoselectivity (dr = 3:1−4:1) was obtained for aldol products bearing quaternary stereogenic centers when α-branched aldehydes, with different substituents at the α-position, were utilized as the donor aldehyde. On the other hand, Avery and Zheng have had success in the synthesis of an epothilone intermediate when the quaternary carbon is part of the acceptor aldehyde.[8] It was noticeable that none of the previously mentioned studies explored disubstituted ketenes as pronucleophiles in the diastereoselective synthesis of β-lactones (aldol surrogates) from chiral aldehydes.[3−10] Moreover, there is a paucity of studies in the literature exploring the aldol reaction of tetrasubstituted enolates/enols/enamines with chiral aldehydes, and so, as a result, application of such aldol reactions to the synthesis of complex molecules containing quaternary carbon centers has been limited.[1,11,12] Indeed, catalytic approaches to aldol reactions (and surrogate aldol reactions) of chiral aldehydes are rare, and the development of such catalytic aldol/aldol-type processes remains a challenging frontier in organic synthesis.[3,7]

In 2010 we reported that an axially chiral phosphine known as Binaphane could catalyze the formal [2 + 2] cycloaddition of alkylarylketenes with mainly aromatic aldehydes (Scheme 1).[5,6] The Binaphane-catalyzed methodology worked best with aromatic aldehydes converting them to β-lactones with good to excellent diastereo- and enantioselectivity. However, aliphatic aldehydes proved to be more problematic, with the level of enantio- and diastereoselectivity being strongly dependent upon the ketene reactant partner. For example, modest diastereoselectivity was obtained with methylphenylketene and ethylphenylketene (dr 2:1 to 3:1), but with ethyl-*N*-methylindolylketene, excellent diastereoselectivity (dr >99:1) and enantioselectivity (93−97% ee) were obtained. Dialkylketenes were also found to be difficult substrates, with modest enantioselectivity and variable diastereoselectivity observed. Within this context, it was by no means certain that phosphine-catalyzed reaction of ketenes with α-chiral aldehydes would proceed satisfactorily.[13] However, we anticipated that the reaction of chiral aldehydes possessing an α-oxy substituent

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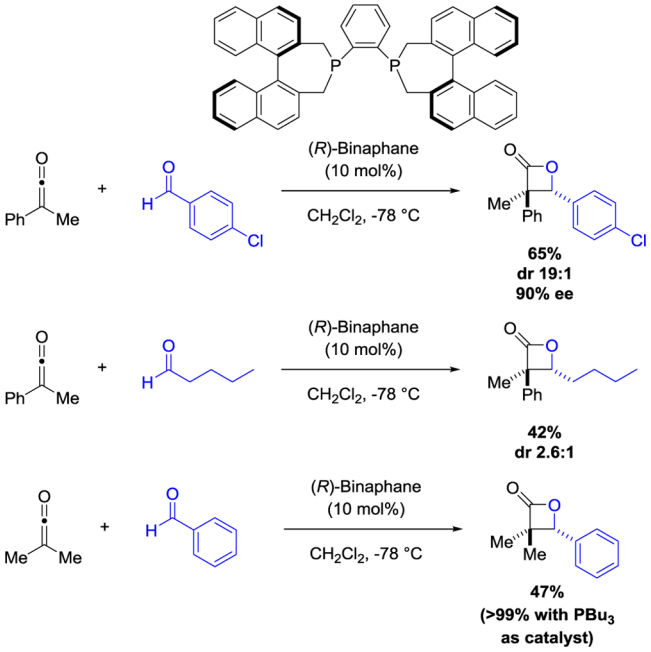
Scheme 1. Our Previous Studies Involving Phosphine Catalysis of [2 + 2] Cycloaddition of Ketenes and Aldehydes

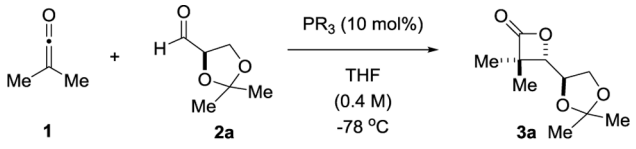


would provide a useful route to biologically interesting complex molecules, e.g. in the synthesis of (+)-peloruside A.[14] We were therefore motivated to investigate the phosphine-catalyzed reaction of disubstituted ketenes with α-chiral oxyaldehydes. In this article we disclose that a catalytic amount of an achiral trialkylphosphine facilitates the formation of β-lactones bearing up to three stereogenic centers, from disubstituted ketenes and chiral aldehydes (possessing α-stereogenic centers), with moderate to excellent diastereoselectivity (dr up to 32:1).

RESULTS AND DISCUSSION

We initiated our studies on the development of the diastereoselective reaction by evaluating a variety of phosphine nucleophilic catalysts for the reaction of dimethylketene with α-chiral aldehyde **2a** (Scheme 2). Although we had previously found (*R*)-Binaphane to be an excellent catalyst for the reaction

Scheme 2. Optimization of Diastereoselective Reaction of Ketenes with α-Chiral Oxyaldehyde



Reaction optimization:

Using Binaphane:
*3 equiv **1**, 1 equiv **2a** conv 15%, dr 9:1*

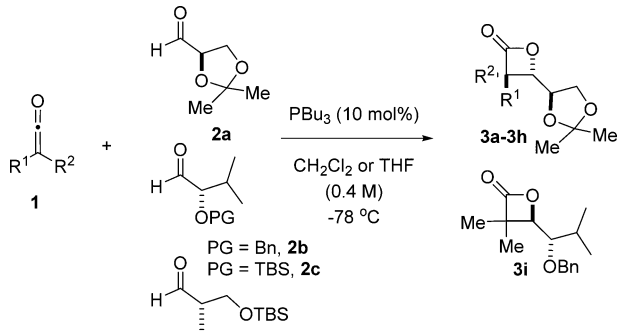
Using PBu_3 (10 mol%):
*1 equiv **1**, 3 equiv **2a** conv 20%, dr 5:1*
*3 equiv **1**, 1 equiv **2a** conv >99% (yield 44%), dr 6:1*
*5 equiv **1**, 1 equiv **2a** yield 32%, dr 8.9:1*
Using PBu_3 (20 mol%):
*3 equiv **1**, 1 equiv **2a** yield 38%, dr 8:1*

of disubstituted ketenes with aromatic aldehydes, it proved to be ineffective with chiral aldehyde **2a** (15% conv).[5,6]

Presumably, the relatively low reactivity of the α-oxy substituted aldehyde coupled with the sterically bulky nature of Binaphane is responsible for the low conversion observed. As we had previously determined trialkylphosphines to be excellent catalysts for the catalytic homodimerization of disubstituted ketenes, and for the catalytic formal [2 + 2] cycloaddition of disubstituted ketenes with aromatic aldehydes, we proceeded to evaluate them for promotion of the reaction involving chiral aldehyde **2a**.[5,6,15,16] Following extensive investigations, it was determined that tri-*n*-butylphosphine was the optimal catalyst, in terms of both conversion and diastereoselectivity (dr = 6:1) (Scheme 2). The moderate isolated yield (typically 40−50%) of β-lactone **3a** was attributed to its acid-sensitive nature and resulting decomposition during silica gel purification. Under some conditions (e.g., when using 20 mol % of PBu_3) a somewhat higher dr of 8:1 to 9:1 could be achieved, albeit with a slightly reduced yield of β-lactone. A range of Lewis acids (e.g., $LiClO_4$ and $Er(OTf)_3$) and some Brønsted acids (e.g., Schreiner's thiourea) were also investigated as additives but always resulted in lower conversion and/or lower diastereoselectivity, or simply a slower reaction rate without any impact on selectivity.

Having developed optimized reaction conditions (10 mol % PBu_3, 1 equiv of aldehyde, 3 equiv of ketene), we then proceeded to investigate the scope of the reaction. A range of dialkylketenes and alkylarylketenes were evaluated in reactions with α-chiral oxysubstituted aldehydes (Table 1). Good to excellent levels of diastereoselectivity were achieved in the reactions of dimethylketene (dr up to 8:1), diethylketene (dr up to 8:1), di-*n*-propylketene (dr 7:1), and diphenylketene (dr

Table 1. Substrate Scope Involving α-Chiral Aldehydes



entry	RCHO	R^1	R^2	% yield[a]	dr[b]	lactone
1	**2a**	Me	Me	44	6:1	**3a**
2	*ent*-**2a**[c]	Me	Me	43	8:1	**3b**
3	**2a**	Et	Et	48	8:1	**3c**
4	*ent*-**2a**	Et	Et	43	7:1	**3d**
5	**2a**	*n*-Pr	*n*-Pr	41	7:1	**3e**
6	*ent*-**2a**	*n*-Pr	*n*-Pr	42	7:1	**3f**
7	*ent*-**2a**	Ph	Ph	59	32:1	**3g**
8	**2a**	*i*-Pr	Me	48	2:1	**3h**
9	**2b**	Me	Me	45	3:1	**3i**
10	**2d**	Ph	Me	<10		

[a]Isolated yield (%) for both diastereomers. [b]dr = diastereomeric ratio represents ratio of major diastereomer to minor diastereomer; determined by GC-MS or ^{1}H NMR analysis of crudes. [c]*ent*-**2a** = enantiomer of **2a**.

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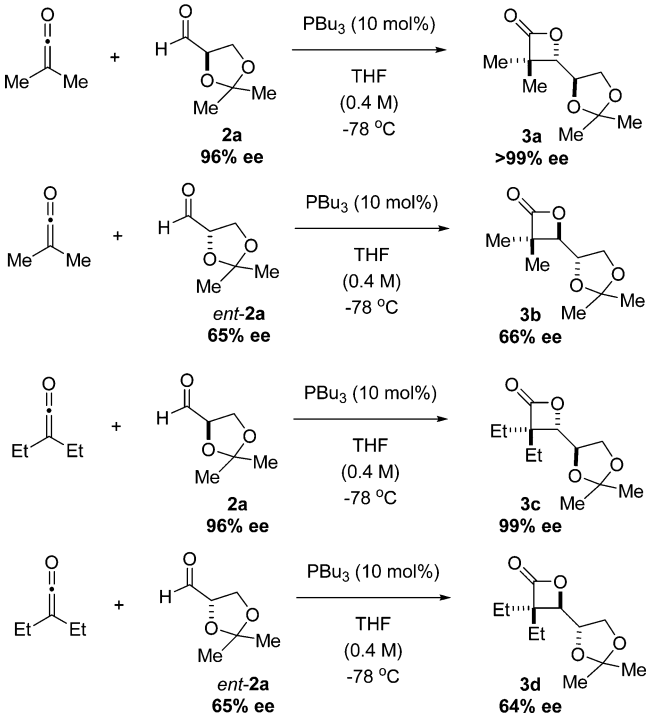
32:1) with glyceraldehyde acetonide. The major diastereomer in these reactions was determined to be the *anti*-diastereomer, based on X-ray crystal structure analysis of **3a**. Assay of the enantiomeric excess of several examples (**3a**−**3d**) revealed no loss or insignificant loss of enantiopurity, and so racemization of aldehyde substrate is not an issue under the reaction conditions (Scheme 3).

Scheme 3. Transfer of Chirality Studies



Much lower diastereoselectivity was obtained in those cases where unsymmetrical ketenes were used (e.g., isopropylmethylketene, entry 8). Methylphenylketene, ethylphenylketene, and *n*-butylphenylketene also performed less successfully (dr 1:1 to 2:1, yields <30%, not shown in Table 1). The low diastereoselectivity observed in these examples is consistent with our earlier Binaphane-catalyzed results involving simple alkylarylketenes and unbranched achiral aliphatic aldehydes (e.g., pentanal) and is in contrast to the generally good selectivity observed in Binaphane-catalyzed reactions of the same ketenes with aromatic aldehydes.[5,6] For aliphatic aldehyde or α-chiral oxysubstituted aldehydes (entry 8 and related) there appears to be poor diastereocontrol (*cis* vs *trans*) for stereogenic centers across the β-lactone ring, and this leads to poor selectivity overall for the creation of three stereogenic centers (e.g., **3h**). Low diastereoselectivity was also observed for some acyclic α-oxysubstituted aldehydes (Table 1 entry 9). Attempts to optimize diastereoselectivity for entry 9 through use of a larger oxy protecting group (TBS) led to slightly improved selectivity (dr 4:1) but at the cost of reaction efficiency (only 40% conv). When PMe_3 was used as the catalyst instead of PBu_3 (in entry 9) for the Bn- and TBS-protected aldehydes, **2b** and **2c**, lower diastereoselectivity (dr 2:1) was obtained and without any significant increase in reaction efficiency. Roche ester derived chiral aldehyde **2d** displayed poor reactivity presumably due to the lack of an α-electron-withdrawing substituent (entry 10).

The observed high levels of diastereoselectivity for most examples (**3a**−**3g**) can be rationalized in terms of a polar Felkin−Anh transition state model.[17] In the lowest energy conformation of the aldehyde, the α-oxy substituent is oriented perpendicular to the carbonyl group, which allows for maximum overlap of the C═O π^* and the α-oxy C−O σ^* molecular orbitals.[17] The nucleophile approaches the carbonyl from a trajectory (along the Bürgi−Dunitz angle) opposite to the sterically large alkoxy substituent to afford the *anti*-diastereomer as the major isomer (Figure 1). Some α-

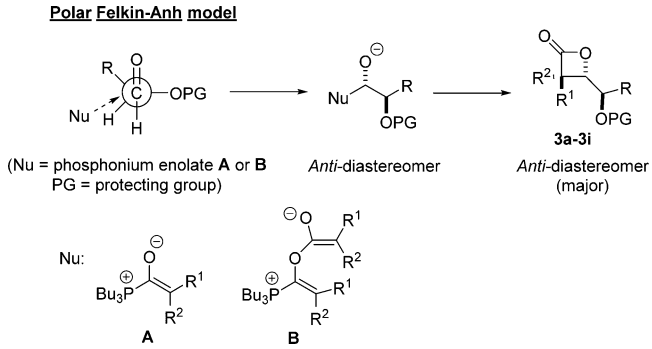


Figure 1. Rationale for diastereoselectivity in phosphine-catalyzed reactions of α-chiral oxyaldehydes.

oxysubstituted aldehydes (Table 1, entry 9) gave somewhat lower diastereoselectivity presumably due to competition between the substituents (OBn vs *i*-Pr) to be the group oriented perpendicular to the aldehyde carbonyl (Figure 1). In addition, using a smaller nucleophile, e.g., enolates derived from PMe_3, led to lower diastereoselectivity (dr 2:1). Lower selectivity in this case is likely due to the relatively smaller (and more reactive) nucleophile encountering less steric interactions, and hence less diastereofacial discrimination, in approaching the carbonyl electrophile. A Cornforth model could also be invoked to explain the high diastereoselectivity observed in most cases.[17c]

Reaction monitoring by ^{31}P NMR analysis suggests that the reactions involve ketene-derived phosphonium enolate intermediates. This agrees with our earlier observations regarding the mechanism operative in phosphine-catalyzed reactions of ketenes with other electrophiles.[6,18] For example, during ^{31}P NMR monitoring at −78 °C of the formation of **3a**, a major signal was observed at 13.0 ppm. This signal is found in a range characteristic of tetravalent phosphonium enolate species.[6,18,19] However, at this point it is not clear whether the key nucleophilic species (Nu) adding to the chiral aldehyde is phosphonium enolate **A** or **B** (Figure 1), and further mechanistic studies will be required to resolve this question.

The results with dimethylketene (Table 1, entries 1 and 2) are of practical interest, given the prevalence of the dimethylated quaternary center structural motif found in natural products, such as (+)-peloruside A, paclitaxel, bryostatin, and the epothilones.[1,14] A demonstration of the power of the phosphine-catalyzed methodology may be ascertained from the asymmetric synthesis of Weinreb amide **5**, which contains the correct stereochemistry and atom connectivity of an intermediate used in the synthesis of (+)-peloruside A (Scheme 4).[14] β-Lactone **3a** was readily converted into **5** (dr >20:1 after purification) in two steps, and so just three steps are required for its synthesis from

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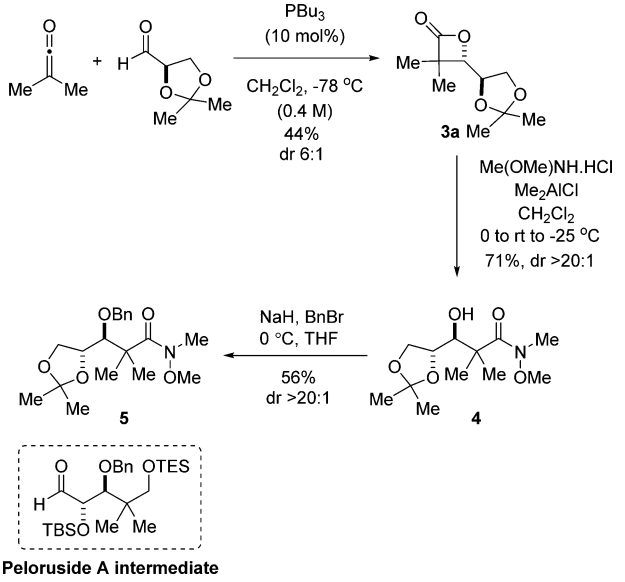
Scheme 4. Asymmetric Synthesis of (+)-Peloruside A Synthon



commercially available (*R*)-glyceraldehyde acetonide (Scheme 4).

CONCLUSION

In summary, we have developed a phosphine-catalyzed diastereoselective reaction of ketenes with α-chiral aldehydes that provides access to chiral β-lactones bearing two stereogenic centers. When PBu_3 was employed as the nucleophilic catalyst the formation of chiral β-lactones bearing two stereogenic centers with moderate to excellent diastereoselectivity (dr $\geq$3:1 for 8 examples, and up to 32:1) was promoted. An example of the utility of the methodology is provided by the asymmetric synthesis of a peloruside A synthon. Future work will involve the design of chiral phosphine catalysts with suitable reactivity for a study of double diastereoselection with chiral aldehydes.

EXPERIMENTAL SECTION

General. THF was freshly distilled from a benzophenone ketyl radical under nitrogen prior to use. *N*,*N*-Dimethylethylamine was distilled from calcium hydride under nitrogen.[20a] Dichloromethane was dried by passing through activated alumina columns on a solvent purification system. Iatrobeads (neutral silica, 60 μM particle size) and TLC plates (UV254, 250 μM) were used as received. Methylphenylketene and diphenylketene were prepared through amine-mediated dehydrohalogenation. Isopropylmethylketene, dimethylketene, diethylketene, and di-*n*-propylketene were prepared through zinc-mediated dehalogenation of the appropriate α-bromoacyl bromide precursor.[20b−d] Tri-*n*-butylphosphine, (*R*)-Binaphane, (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde ((*S*)-**2a**: 65% ee), and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde ((*R*)-**2a**: 96% ee) were purchased and used as received. (2*S*)-2-Benzyloxy-3-methylbutanal (**2b**; $[\alpha]_D^{24} = -78.1$ (c = 0.91, CH_2Cl_2); Reported $[\alpha]_D^{24} = -90.2$ (c = 0.96, CH_2Cl_2)) and aldehyde **2c** were prepared as per literature procedure starting from commercial (*S*)-(+)-2-hydroxy-3-methylbutyric acid.[2d] Aldehyde **2d** was prepared from Roche ester though a procedure described by Burgess's group.[21]

NMR spectra were recorded on a 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra. High resolution mass spectra were obtained on an Accurate Mass Q-TOF LC-MS instrument with ESI as the ionization method. Low resolution mass spectra were recorded on a GC-MS instrument with a mass selective detector, and using a GC column (30 m, 0.25 mm ID). IR spectra were recorded on an IR spectrometer.

Compound Characterization and Determination of Diastereomeric Ratios and Enantiomeric Excesses. The β-lactones **3** were purified by plug column chromatography through neutral silica to provide samples of high purity for full characterization. Diastereomeric ratios were determined for the crude β-lactones **3a**−**3i** by integrating the tertiary C**H** resonances on the β-lactones in ^{1}H NMR spectra or by GC-MS analysis.

Procedure A for β-Lactone Synthesis. To a stirring solution of aldehyde (1 equiv) and phosphine catalyst (PBu_3 in most cases) (0.1 equiv) in THF (amount specified for each example) at −78 °C under a nitrogen atmosphere was added a solution of ketene (3 equiv) in THF (amount specified for each example) in one portion. The reaction was stirred at −78 °C for another 8 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 (Iatrobeads, 2.5 cm × 3.0 cm, 6 g) [ca. 50 × 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 **3** in high purity (≥95%) in most cases.

Procedure B for β-Lactone Synthesis. To a stirring solution of aldehyde (1 equiv) and phosphine catalyst (PBu_3 in most cases) (0.1 equiv) in dichloromethane (amount specified for each example) at −78 °C under a nitrogen atmosphere was added a solution of ketene (1 equiv) in dichloromethane (amount specified for each example) 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). Purification was the same as that for Procedure A.

(*S*)-3,3-Dimethyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-oxetan-2-one (3a). By following Procedure A, dimethylketene (565 mg, 8.07 mmol) in THF (5 mL) was added to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (350 mg, 2.69 mmol, 96% ee) and *n*-Bu_3P (54 mg, 0.269 mmol) in THF (1.7 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3a** as a white crystal-like solid (237 mg, 44%), dr 6:1 (by ^{1}H NMR and GC-MS); Chiral GC analysis: >99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3−18.5 psi; oven temperature: 50−180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 61.7 min (major)]; $[\alpha]_D^{24} = 11.5$ (c = 0.13, CH_2Cl_2); IR (CH_2Cl_2): 2985, 2937, 2880, 1831, 1467, 1373, 1256, 1227, 1214, 1191, 1144, 1094, 1069, 961, 947, 905, 859, 842, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.27−4.20 (m, 1H), 4.18−4.12 (m, 1H), 4.05 (d, J = 9.3 Hz, 1H), 3.97 (dd, J = 8.4, 4.0 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 110.5, 81.0, 74.2, 67.4, 54.5, 27.3, 25.4, 22.9, 16.7; $(M+H)^+$ HRMS m/z calcd for $(C_{10}H_{17}O_4)^+$: 201.1127; Found: 201.1122.

(*R*)-3,3-Dimethyl-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-oxetan-2-one (3b). Following Procedure A, dimethylketene (194 mg, 2.77 mmol) in THF (1.8 mL) was added to (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (120 mg, 0.92 mmol, 65% ee) and *n*-Bu_3P (19 mg, 0.092 mmol) in THF (0.5 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3b** as a white crystal-like solid (79 mg, 43%), dr 8:1 (by ^{1}H NMR and GC-MS); Chiral GC analysis: 66% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3−18.5 psi ; oven temperature: 50−180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 62.0 min (minor), 68.4 min (major)]; $[\alpha]_D^{24} = -10.4$ (c = 1.4, CH_2Cl_2); IR (CH_2Cl_2): 2984, 2937, 1829, 1467, 1372, 1256, 1214, 1067, 946, 904, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.27−4.20 (m, 1H), 4.18−4.13 (m, 1H), 4.05 (d, J = 9.3 Hz, 1H), 3.97 (dd, J = 8.8, 4.0 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 110.5, 81.0, 74.2, 67.4, 54.5, 27.3, 25.4, 22.9, 16.7;

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$(M + H)^+$ HRMS m/z calcd for $(C_{10}H_{17}O_4)^+$: 201.1127; Found: 201.1124.

(*S*)-3,3-Diethyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)oxetan-2-one (3c). By following Procedure A, diethylketene (127 mg, 1.29 mmol) in THF (0.8 mL) was added to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (56 mg, 0.43 mmol, 96% ee) and *n*-Bu_3P (9 mg, 0.043 mmol) in THF (0.3 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3c** as a colorless oil (46 mg, 48%), dr 8:1 (by ^1H NMR and GC-MS); Chiral GC analysis: 99% ee [Supelco Chiraldex BDM column; GC conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3−18.5 psi; oven temperature: 50−180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 77.5 min (major), 79.2 min (minor)]; $[\alpha]_D^{24}$ = 1.95 (c = 2.2, CH_2Cl_2); IR (CH_2Cl_2): 2971, 2881, 1826, 1459, 1372, 1256, 1211, 1067, 950, 899, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.32−4.25 (m, 1H), 4.19−4.13 (m, 1H), 4.07 (d, J = 9.3 Hz, 1H), 3.98 (dd, J = 9.0, 4.2 Hz, 1H), 1.98−1.74 (m, 4H), 1.43 (s, 3H), 1.35 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 110.5, 79.7, 73.3, 67.5, 62.7, 27.2, 25.3, 24.7, 20.6, 8.5, 8.5; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{21}O_4)^+$: 229.1440; Found: 229.1438.

(*R*)-3,3-Diethyl-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)oxetan-2-one (3d). By following Procedure A, diethylketene (138 mg, 1.40 mmol) in THF (0.8 mL) was added to (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (61 mg, 0.47 mmol, 65% ee) and *n*-Bu_3P (9 mg, 0.047 mmol) in THF (0.4 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3d** as a colorless oil (46 mg, 43%), dr 7:1 (by ^1H NMR and GC-MS); Chiral GC analysis: 64% ee [Supelco Chiraldex BDM column; GC conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3−18.5 psi; oven temperature: 50−180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 77.8 min (minor), 79.6 min (major)]; $[\alpha]_D^{24}$ = −0.45 (c = 2.9, CH_2Cl_2); IR (CH_2Cl_2): 2972, 2881, 1826, 1459, 1372, 1256, 1212, 1067, 950, 899, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.32−4.25 (m, 1H), 4.19−4.13 (m, 1H), 4.07 (d, J = 9.5 Hz, 1H), 3.98 (dd, J = 9.0, 4.2 Hz, 1H), 1.99−1.73 (m, 4H), 1.43 (s, 3H); 1.35 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 110.5, 79.7, 73.3, 67.5, 62.7, 27.2, 25.3, 24.7, 20.6, 8.5, 8.5; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{21}O_4)^+$: 229.1440; Found: 229.1437.

(*S*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3-dipropyloxetan-2-one (3e). By following Procedure A, di-*n*-propylketene (276 mg, 2.19 mmol) in THF (1.3 mL) was added to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (95 mg, 0.73 mmol) and *n*-Bu_3P (15 mg, 0.073 mmol) in THF (0.5 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3e** as a colorless oil (77 mg, 41%), dr 7:1 (by ^1H NMR and GC-MS); $[\alpha]_D^{24}$ = 0.24 (c = 2.5, CH_2Cl_2); IR (CH_2Cl_2): 2960, 2875, 1829, 1467, 1373, 1254, 1213, 1143, 1067, 901, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.32−4.25 (m, 1H), 4.19−4.12 (m, 1H), 4.07 (d, J = 9.4 Hz, 1H), 3.97 (dd, J = 9.0, 4.1 Hz, 1H), 1.86−1.62 (m, 4H), 1.59−1.42 (m, 3H), 1.43 (s, 3H); 1.36 (s, 3H), 1.36−1.24 (m, 1H), 1.01−0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 110.5, 79.9, 73.3, 67.4, 61.9, 34.6, 30.1, 27.1, 25.3, 17.6, 17.4, 14.8, 14.5; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{25}O_4)^+$: 257.1753; Found: 257.1748.

(*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3-dipropyloxetan-2-one (3f). By following Procedure A, di-*n*-propylketene (338 mg, 2.67 mmol) in THF (1.7 mL) was added to (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (116 mg, 0.89 mmol) and *n*-Bu_3P (18 mg, 0.089 mmol) in THF (0.5 mL). Elution with 4% EtOAc/hexane through a plug column of neutral silica gel afforded **3f** as a colorless oil (95 mg, 42%), dr 7:1 (by ^1H NMR and GC-MS); $[\alpha]_D^{24}$ = −0.62 (c = 2.9, CH_2Cl_2); IR (CH_2Cl_2): 2960, 2875, 1825, 1467, 1372, 1256, 1212, 1066, 971, 899, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 4.32−4.25 (m, 1H), 4.19−4.12 (m, 1H), 4.07 (d, J = 9.5 Hz, 1H), 3.98 (dd, J = 8.9, 4.1 Hz, 1H), 1.86−1.62 (m, 4H), 1.58−1.41 (m, 3H), 1.43 (s, 3H); 1.36 (s, 3H), 1.36−1.24 (m, 1H), 1.01−0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 110.5, 79.9, 73.3, 67.5, 62.0, 34.7, 30.2, 27.2, 25.3, 17.6, 17.5, 14.8, 14.5; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{25}O_4)^+$: 257.1753; Found: 257.1750.

(*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,3-diphenyloxetan-2-one (3g). By following Procedure B, diphenylketene (50 mg, 0.26 mmol) in CH_2Cl_2 (0.7 mL) was added to (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (67 mg, 0.52 mmol) and *n*-Bu_3P (10 mg, 0.052 mmol) in CH_2Cl_2 (0.6 mL). Elution with 3% EtOAc/hexane through a plug column of neutral silica gel afforded **3g** as a colorless oil (49 mg, 59%), dr 32:1 (by ^1H NMR and GC-MS); $[\alpha]_D^{24}$ = −97.3 (c = 1.5, CH_2Cl_2); IR (CH_2Cl_2): 2987, 1827, 1495, 1450, 1381, 1256, 1127, 905, 840, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.52−7.47 (m, 2H), 7.44−7.25 (m, 8H), 5.11−5.05 (m, 1H), 4.01−3.91 (m, 2H), 3.88−3.8 (m, 1H), 1.54 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 137.9, 134.6, 128.2, 128.0, 127.3, 127.2, 127.0, 126.0, 109.5, 80.3, 72.7, 70.7, 65.3, 26.1, 24.4; $(M + H)^+$ HRMS m/z calcd for $(C_{20}H_{21}O_4)^+$: 325.1440; Found: 325.1439.

(3*S*,4*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-isopropyl-3-methyloxetan-2-one (3h). By following Procedure A, isopropylmethylketene (86 mg, 0.88 mmol) in THF (0.6 mL) was added to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (38 mg, 0.29 mmol) and *n*-Bu_3P (6 mg, 0.029 mmol) in THF (0.2 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3h** as a white solid (32 mg, 48% yield), dr = 2:1 (by GC-MS); IR (CH_2Cl_2): 2967, 2935, 2879, 1811, 1464, 1374, 1275, 1260, 1214, 1144, 1113, 1067, 970, 946, 932, 906, 885, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 4.41−4.31 (dt, J = 11.4, 5.7, 3.5 Hz, 1H), 4.21−4.14 (dd, J = 8.9, 6.1 Hz, 1H), 4.09 (d, J = 9.2 Hz, 1H), 4.00−3.92 (dd, J = 8.8, 5.3 Hz, 1H), 2.42−2.30 (m, 1H), 1.45 (s, 3H); 1.40 (s, 3H); 1.39 (s, 3H), 1.14 (d, J = 8.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer: δ 174.1, 110.7, 83.2, 72.8, 67.5, 61.9, 31.8, 27.4, 25.6, 22.9, 17.9, 14.7; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{21}O_4)^+$: 229.1440; Found: 229.1432.

(*R*)-4-((*S*)-1-(Benzyloxy)-2-methylpropyl)-3,3-dimethyloxetan-2-one (3i). By following Procedure A, dimethylketene (109 mg, 1.56 mmol) in THF (1.0 mL) was added to (2*S*)-2-benzyloxy-3-methylbutanal (100 mg, 0.52 mmol) and *n*-Bu_3P (11 mg, 0.052 mmol) in THF (0.3 mL). Elution with 3% EtOAc/hexane through a plug column of neutral silica gel afforded **3i** (major isomer) as a colorless oil (55 mg, 40%) and **3i** (minor isomer) as a colorless oil (7 mg, 5%), dr 3:1 (by ^1H NMR and GC-MS); Major isomer: $[\alpha]_D^{24}$ = 17.1 (c = 4.5, CH_2Cl_2); IR (CH_2Cl_2): 2962, 2875, 1827, 1465, 1388, 1095, 1067, 910, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.40−7.26 (m, 5H), 4.65 (d, J = 11 Hz, 1H), 4.58 (d, J = 11 Hz, 1H), 4.29 (d, J = 7.3 Hz, 1H), 3.59 (dd, J = 7.4, 4.7 Hz, 1H), 2.16−2.04 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.10−1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 137.4, 127.7, 127.0, 126.8, 81.4, 80.6, 72.9, 53.6, 29.0, 22.6, 18.0, 17.3, 16.6; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{23}O_3)^+$: 263.1647; Found: 263.1644.

Minor isomer: $[\alpha]_D^{24}$ = 9.71 (c = 0.7, CH_2Cl_2); IR (CH_2Cl_2): 2967, 2877, 1827, 1466, 1391, 1180, 906, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38−7.26 (m, 5H), 4.82 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 4.38 (d, J = 8.7 Hz, 1H), 3.49 (dd, J = 8.9, 2.5 Hz, 1H), 1.79−1.69 (m, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 138.8, 128.5, 128.1, 127.8, 84.6, 81.8, 74.5, 53.9, 30.1, 22.8, 20.4, 17.4, 16.4; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{23}O_3)^+$: 263.1647; Found: 263.1642.

(*S*)-3-Hydroxy-*N*-methoxy-*N*,2,2-trimethyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanamide (4). A dimethylaluminum chloride (1.0 mL, 1.0 mmol) solution (1 M in hexane) was added dropwise to an ice cooled stirring mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (97.5 mg, 1.0 mmol) in CH_2Cl_2 (6 mL). After 10 min the reaction was removed from the ice bath, and stirring was continued at room temperature. After 2 h of stirring at room temperature, the clear solution was cooled to −25 °C and a solution of **3g** (100 mg, 0.5 mmol, dr 6:1, >99% ee) in CH_2Cl_2 (3 mL) was added, with continued stirring at −25 °C for 16 h. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (2 mL), diluted with water (25 mL), acidified with 2 N HCl to pH ∼7,

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and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by silica gel column chromatographic purification using 40% EtOAc/hexane afforded **4** as a colorless viscous oil (93 mg, 71%), dr >20:1 (by ^{1}H NMR); $[\alpha]_D^{24}$ = 1.93 (c = 1.6, CH_2Cl_2); IR (CH_2Cl_2): 3434, 2983, 2935, 1625, 1369, 1257, 1210, 1155, 1052, 995, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 4.21−4.13 (m, 1H), 4.12−4.05 (m, 1H), 4.02−3.95 (m, 1H), 3.81 (t, J = 6.8 Hz, 1H), 3.71 (s, 3H) 3.34 (d, J = 6.8 Hz, 1H), 3.19 (s, 3H), 1.40 (s, 3H); 1.34 (s, 6H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 109.1, 78.5, 76.7, 67.6, 61.0, 47.0, 34.0, 26.8, 25.9, 22.2, 21.2; (M + H)$^+$ HRMS m/z calcd for $(C_{12}H_{24}NO_5)^+$: 262.1654; Found: 262.1656.

(*S*)-3-(Benzyloxy)-*N*-methoxy-*N*,2,2-trimethyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanamide (5). To an ice-cooled stirring suspension of sodium hydride (22 mg, 0.45 mmol) in THF (4 mL) was added a solution of **4** (78 mg, 0.29 mmol) in THF (2 mL) dropwise. After 15 min of stirring, benzyl bromide (102 mg, 0.59 mmol) was added to the reaction mixture and stirring was continued at 0 °C for 1 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (2 mL), diluted with water (25 mL), and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by silica gel column chromatographic purification using 30% EtOAc/hexane afforded **5** as a colorless viscous oil (59 mg, 56%), dr >20:1 (by ^{1}H NMR); $[\alpha]_D^{24}$ = −4.5 (c = 2.8, CH_2Cl_2); IR (CH_2Cl_2): 2983, 2935, 1647, 1454, 1209, 1060, 997, 865, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38−7.26 (m, 5H), 4.85 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 3.0 Hz, 1H), 4.17−4.09 (m, 1H), 4.04 (t, J = 7.7 Hz, 1H), 3.98 (t, J = 7.8 Hz, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 1.43 (s, 3H); 1.33 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 139.0, 128.5, 127.9, 127.7, 108.0, 81.6, 77.3, 75.3, 65.5, 60.8, 47.6, 34.3, 26.6, 25.0, 22.9, 21.0; (M + H)$^+$ HRMS m/z calcd for $(C_{19}H_{30}NO_5)^+$: 352.2124; Found: 352.2127.

Determination of Relative Stereochemistry for 3a−3i. The major diastereomer of the α-chiral aldehyde-derived β-lactone **3a** was crystallized from EtOAc/hexane and determined to be the *anti*-isomer by X-ray crystal structure analysis (see CIF **3a**). By analogy, the major diastereomer of lactones **3b−3i** was assigned the *anti* relative configuration.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data for all new compounds, chromatograms for **3a−3d**, CIF for lactone **3a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00869.

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Notes

The authors declare no competing financial interest.

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