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Phosphine-Catalyzed Asymmetric Synthesis of β-Lactones from Disubstituted Ketenes and Aldehydes

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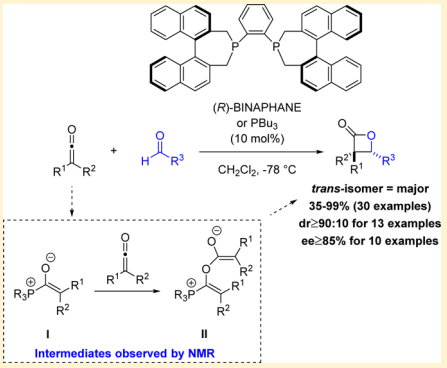
Supporting Information

ABSTRACT: In this article we describe a general catalytic procedure for the formation of β-lactones bearing two stereogenic centers, from disubstituted ketenes and achiral aldehydes. BINAPHANE was found to display excellent enantioselectivity (≥90% ee for eight examples) and good diastereoselectivity (≥90:10 for 13 examples) in catalyzing the formation of β-lactones bearing two stereogenic centers from achiral aldehydes (both aromatic and aliphatic) and alkylarylketenes or dialkylketenes. A preference for formation of the trans diastereomer was observed in these reactions. For those reactions where BINAPHANE failed as a catalyst, tri-*n*-butylphosphine was found to be an effective achiral nucleophilic catalyst, effecting good yield and diastereoselectivity in racemic β-lactone formation. Evidence for the involvement of phosphonium enolate intermediates in the reaction mechanism was obtained through reaction monitoring by ^{31}P NMR spectroscopy and by comparison with previously characterized intermediates observed in the phosphine-catalyzed ketene homodimerization reaction.



INTRODUCTION

β-Lactones are regarded as highly prized small molecules due to their potential for use as intermediates in synthetic activities and because of their presence as integral components of many important drug molecules.[1,2] In recent years many catalytic asymmetric synthetic approaches to β-lactones have been introduced, with chiral Lewis acid and chiral nucleophile-catalyzed approaches being the most prominent and most successful.[3] Wynberg's group was the first to demonstrate that β-lactones could be formed in very high enantiomeric excesses (>90% ee) through the use of an organic nucleophilic catalyst. In what was a seminal moment in the development of organocatalysis, they discovered that cinchona alkaloid catalysts gave the best results in promoting the formal [2 + 2] cycloaddition of ketene with a highly activated aldehyde, chloral.[4] Over the following 25 years, a number of groups used the basic template of an alkaloid catalyst to develop improved methodologies for the asymmetric synthesis of β-lactones. In particular, the groups of Romo, Nelson, and Calter made impressive contributions to extend the utility of the formal [2 + 2] cycloaddition of a ketene with an aldehyde to include less activated, and more synthetically useful, aldehydes.[5−7] The addition of mild Lewis acids, in combination with an alkaloid catalyst, was shown by some of these groups to be beneficial with regard to expansion of substrate scope.[6,7] However, alkaloid catalysis has clear limitations in that only certain ketene substrates can be tolerated. Ketene and simple monosubstituted alkylketenes (usually methylketene or alkoxyketenes) work best as substrates, most likely due to the attenuated nucleophilicity of derived ammonium enolates (or low equilibrium concentrations of enolates). Fu's group was the first to show that enantioenriched β-lactones could be generated from *disubstituted* ketenes through a catalytic asymmetric approach. In their system a planar chiral azaferrocene catalyst catalyzed the enantioselective reaction of dialkylketenes with aromatic aldehydes, albeit with moderate diastereoselectivity. Unfortunately, Fu's system was not successful with alkylarylketenes or with aliphatic aldehydes.[8] Ye's group later reported a chiral N-heterocyclic carbene catalyzed formal cycloaddition of alkylarylketenes with highly activated 2-oxoaldehydes.[9] Smith's group have also recently disclosed their results using a chiral N-heterocyclic carbene catalyst to catalyze the reaction of alkylarylketenes with highly activated nitrobenzaldehydes and pyridinecarboxaldehydes.[10] However, both Ye's and Smith's groups found that more electron rich aromatic aldehydes were not tolerated as substrates.[9,10]

For a number of years, we have pursued a program of research investigating phosphines as nucleophilic catalysts for reactions of ketenes, with the goal of developing new reactions and improving the scope of existing reactions. For the synthesis of highly substituted β-lactones, via a formal [2 + 2] cycloaddition of disubstituted ketenes and aldehydes, we anticipated that a phosphine catalytic system would compare favorably or surpass other systems from a reactivity standpoint. This would be expected due to the superior polarizability of the phosphorus atom in phosphines relative to that of the nitrogen atom in amines.[11] We were also confident of developing a

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highly enantioselective variant of the reaction, given the success that other groups had demonstrated in the phosphine-catalyzed reactions of related cumulenes, such as allenoates.[12]

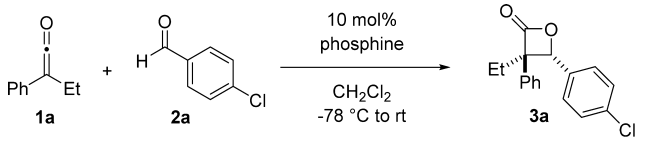
In 2010 we reported that the axially chiral phosphine, BINAPHANE, could catalyze the formal [2 + 2] cycloaddition of alkylarylketenes with mainly aromatic aldehydes.[13] Recently, we broadened the scope of this study to investigate the BINAPHANE-catalyzed reaction of alkylarylketenes with aliphatic aldehydes and of dialkylketenes in reaction with aromatic aldehydes, as well as completing our examination of the reaction of alkylarylketenes with aromatic aldehydes. In those cases where BINAPHANE failed as a catalyst, PBu_3 was investigated as an achiral nucleophilic catalyst for the diastereoselective synthesis of racemic β-lactones. A comprehensive examination of the BINAPHANE/PBu_3 system's scope with regard to aldehyde type (aromatic and aliphatic) and ketene type (alkylarylketene and dialkylketene) was therefore carried out and is described in this paper. A series of mechanistic experiments was also designed, and on the basis of the results of those studies, a discussion of the most likely mechanism of the reaction is presented.

RESULTS AND DISCUSSION

For reaction optimization, we chose a moderately reactive alkylarylketene, ethylphenylketene, and a weakly activated aromatic aldehyde, 4-ClPhCHO, as test substrates (Table 1).[13,14] Not surprisingly, it was found necessary to add the ketene solution slowly to the phosphine solution in order to obtain optimal yields/conversions of the desired β-lactone. This is because phosphines, especially trialkylphosphines, act as excellent nucleophilic catalysts for the homodimerization of disubstituted ketenes, and so it was essential to keep the concentration of the ketene low.[14] When the reaction was carried out in the presence of Lewis acids (e.g., LiI), poor diastereoselectivity was observed, and so systems involving Lewis acid additives were not evaluated further.[6,7] A diverse array of chiral phosphine nucleophilic catalysts that had previously shown success in related reactions was then evaluated—this included those containing central chirality (DUANPHOS, Duphos, and Josiphos), as well as examples of molecules displaying axial chirality (BINAPHANE and related phosphepines), and planar chirality (Josiphos).[12,14,15] (*R*)-BINAPHANE was determined to be the best catalyst when the key factors of reactivity, diastereoselectivity, and enantioselectivity were considered (Table 1, entry 7).[13] Surprisingly, the related monophosphepines **5** and **6** were found to give significantly lower levels of asymmetric induction than BINAPHANE. Therefore, it appears that steric interactions imposed by an ortho-substituted aryl group on the diphosphepine phosphorus atom are necessary for reasonably high levels of enantioselection (>60% ee). Interestingly, a completely different type of catalyst, Josiphos, was found to catalyze the reaction with very good enantioselectivity (90% ee), but unfortunately with poor diastereoselectivity, and so was not investigated any further (entry 5).

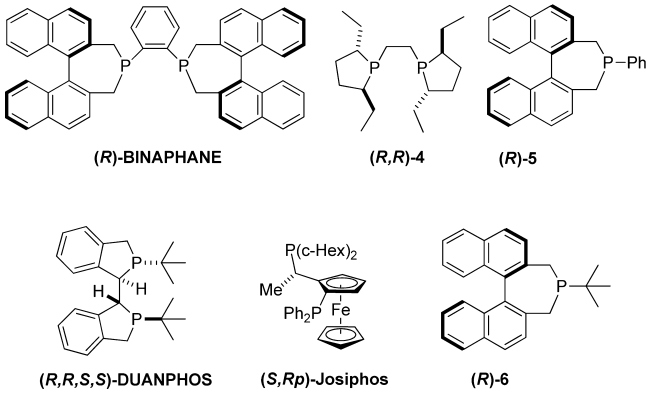
Having identified BINAPHANE as an appropriate asymmetric catalyst for further study, we then proceeded to evaluate the substrate scope of the chiral phosphine system (Table 2). Due to incomplete conversion in many cases and to facilitate compound isolation and characterization, many isolated yields for examples in Table 2 were determined following ring opening of crude β-lactones **3** with aqueous KOH. The derived β-hydroxycarboxylic acids **7** were obtained as analytically pure

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



entry	catalyst[a]	addition time of **1a**	conversn, %[b] (yield, %)	dr[c]	ee, %[d]
1	PBu_3	direct	20	90:10	
2	PBu_3	4 h	91	95:5	
3	PBu_3/LiI (0.3 equiv)	direct	>99	60:40	
4	Duanphos	4 h	0		
5	Josiphos	4 h	(19)	56:44	90
6	(*R*,*R*)-**4**	4 h	6	71:29	
7	(*R*)-BINAPHANE	4 h	(94)	93:7	64
8	(*R*)-Ph-phosphepine **5**	4 h	(63)	92:8	32
9	(*R*)-*t*-Bu-phosphepine **6**	4 h	(42)	80:20	31

[a]Structures of catalysts:



[b]conversn = conversion to **3a**; yield is isolated yield for **3a**. [c]Diastereomeric ratio (dr) determined by GC-MS or ^{1}H NMR analysis of crude product. [d]ee determined by chiral HPLC analysis.

compounds.[13] The relative stereochemistry of β-lactones **3** was determined to be trans through X-ray crystallographic analysis of (±)-**3d**.[13] We (and others)[8,9] have defined the "trans" diastereomer of the trisubstituted β-lactone **3** to represent the isomer with the highest priority groups at each stereogenic center on opposite sides of the β-lactone ring, while the "cis" diastereomer represents the isomer with the highest priority groups at each stereogenic center on the same side of the β-lactone ring. Given that most catalytic asymmetric cycloaddition methods for β-lactone synthesis favor formation of the cis diastereomer, the phosphine-catalyzed methodology fulfills an important role in providing direct access to the less readily accessible trans diastereomer.[6−10]

A range of structurally diverse alkylarylketenes were examined, with the best results in terms of enantioselectivity and diastereoselectivity being obtained with methylphenylketene and ethyl-*N*-methyl-3-indolylketene (entries 2, 3, and 17). Ethyl-*N*-methyl-3-indolylketene proved to be a remarkable substrate, with >90% ee being obtained for all β-lactone examples derived from it (Tables 1 and 2). Moreover, it was especially noteworthy that the system was found to be tolerant of very stable ketene substrates, such as diphenylketene (entry

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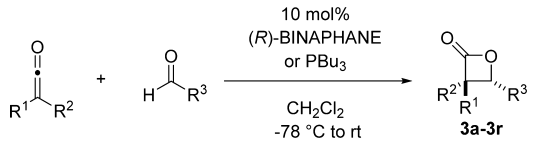
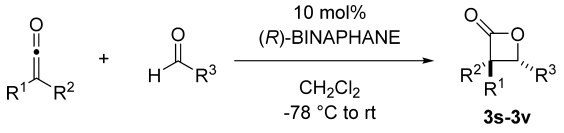
Table 2. Substrate Scope of Phosphine-Catalyzed Formal [2 + 2] Cycloaddition: Alkylarylketenes and Aromatic Aldehydes



entry	R^1	R^2	R^3	yield, %[a]	dr[b]	ee, %	lactone
1	Ph	Me	Ph	87	96:4	79	**3b**
2	Ph	Me	4-ClPh	65	95:5	90	**3c**
3	Ph	Me	4-NO_2Ph	63	94:6	92	**3d**
4[c]	Ph	Me	2-NO_2Ph	35[d]	69:31		**3e**
5[c]	Ph	Me	2-FPh	56[d]	65:35		**3f**
6[c]	Ph	Me	2-ClPh	39[d]	62:38		**3g**
7[c]	Ph	Me	3-ClPh	49[d]	>99:1		**3h**
8	Ph	Et	2-ClPh	>99[d]	75:25	nd	**3i**
9	Ph	Et	4-ClPh	94[d]	93:7	64	**3a**
10	Ph	Et	4-NO_2Ph	51	80:20	87	**3j**
11	Ph	*n*-Bu	4-ClPh	58	92:8	41/>99	**3k**
12	Ph	*n*-Bu	4-NO_2Ph	99	53:47	61/96	**3l**
13	2-tolyl	Me	4-NO_2Ph	72	96:4	54	**3m**
14	4-tolyl	Me	4-ClPh	72	92:8	84	**3n**
15	4-tolyl	Me	4-NO_2Ph	55	90:10	85	**3o**
16[c]	4-tolyl	Me	3-ClPh	37[d]	>99:1		**3p**
17	indolyl[e]	Et	4-ClPh	75	83:17	>99	**3q**
18	Ph	Ph	4-NO_2Ph	62[d]		96	**3r**

[a]Isolated yield for *β*-hydroxyacid **7** derived from *β*-lactone **3** unless stated otherwise. [b]Diastereomeric ratio (dr) determined by GCMS and ^{1}H NMR analysis of crude product. [c]10 mol % PBu_3 used as catalyst. [d]Isolated yield for *β*-lactone **3**. [e]indolyl = *N*-methyl-3-indolyl.

Table 3. Substrate Scope of Phosphine-Catalyzed Formal [2 + 2] Cycloaddition: Alkylarylketenes and Aliphatic Aldehydes



entry	R^1	R^2	R^3	yield, %[a]	dr[b]	ee, %	lactone
1	Ph	Me	$(CH_2)_3CH_3$	42	72:28	nd	**3s**
2	Ph	Et	$(CH_2)_3CH_3$	83	65:35	nd	**3t**
3[c]	indolyl	Et	CH_2CH_2Ph	61	>99:1	97	**3u**
4[c]	indolyl	Et	$(CH_2)_3CH_3$	59	>99:1	93	**3v**

[a]Yield is isolated yield for both diastereomers of **3** or derived *β*-hydroxy acid **7**. [b]Diastereomeric ratio (dr) determined by GCMS and ^{1}H NMR analysis of crude product. [c]indolyl = *N*-methyl-3-indolyl.

18).[16] Electron-deficient aromatic aldehydes, where the electron-withdrawing substituent was Cl or NO_2, gave optimal levels of diastereoselectivity and enantioselectivity (e.g., entries 2, 3, 14, and15).[16] However, even in the absence of an electron-withdrawing group on the aromatic ring of the aldehyde (as in the case of benzaldehyde), good diastereoselectivity and enantioselectivity could be obtained, providing a ketene of appropriate reactivity (methylphenylketene) was used as reactant partner (entry 1). With a less reactive ketene, such as ethylphenylketene, much lower enantioselectivity was observed when it was subjected to reaction with benzaldehyde. Poor to moderate diastereoselectivity was observed in cases where an ortho-substituted aromatic aldehyde was used (Table 2, entries 4−6, and 8). In addition, diastereoselectivity was found to decrease as the ketene alkyl substituent became progressively longer, with *n*-butylphenylketene giving substantially worse results than ethylphenylketene, which in turn gave worse results than methylphenylketene (e.g., entry 12 vs entry 10 vs entry 3). This decrease in diastereoselectivity may be attributed to competing reaction mechanisms (see Schemes 1 and 5), or more likely to increased reversibility of aldolate formation (retro-aldol reaction; see Scheme 5). In some cases low reactivity was shown by BINAPHANE, and so only racemic product could be obtained through the PBu_3-catalyzed reaction (e.g., entry 4). 3-Thiophenecarboxaldehyde underwent a smooth reaction with methylphenylketene to give the desired *β*-lactone, but it underwent decarboxylation during silica gel purification to give the corresponding alkene in good yield (82%) and with high *E* selectivity (89:11). This was also the case with *α*,*β*-unsaturated aldehydes, such as cinnamaldehyde.

The scope of the phosphine-catalyzed methodology with respect to the reaction of alkylarylketenes with aliphatic aldehydes was then investigated (Table 3). Aliphatic aldehydes were investigated, as they represent an important class of aldehydes with regard to the potential use of the methodology in natural product synthesis.[6] The level of enantioselectivity and diastereoselectivity observed was strongly dependent upon the ketene partner used in these reactions. When ethyl-*N*-methyl-3-indolylketene was used as a reactant partner (entries 3 and 4, Table 3), excellent levels of asymmetric induction (>90% ee)

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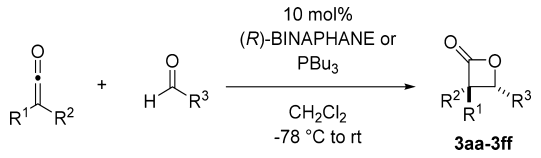
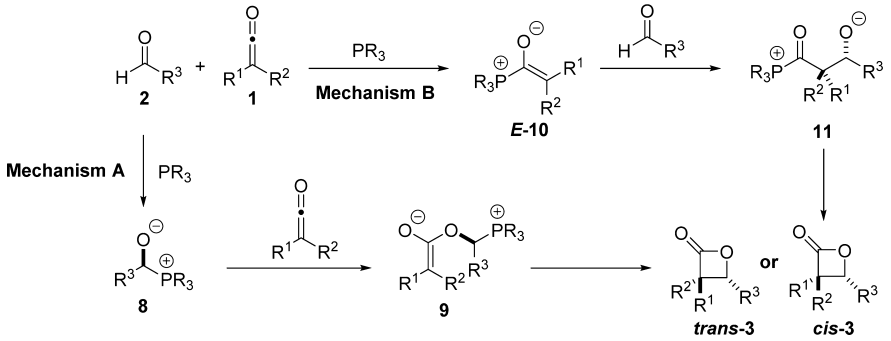
Table 4. Substrate Scope of Phosphine-Catalyzed Formal [2 + 2] Cycloaddition: Dialkylketenes and Aromatic Aldehydes



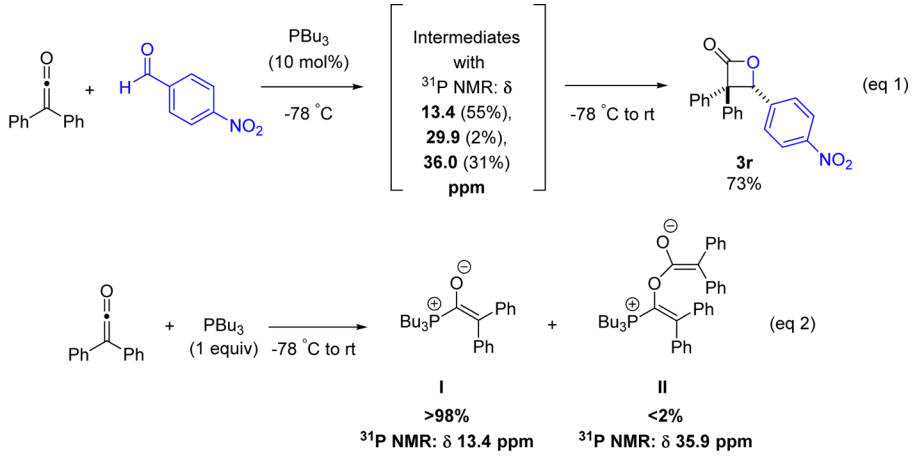
entry	cat.	R^1	R^2	R^3	yield, %[a]	dr[b]	ee, %	lactone
1	PBu_3	Me	Me	Ph	>99			**3aa**
2	(*R*)-BINAPHANE	Me	Me	Ph	47		22	**3aa**
3	PBu_3	Me	Me	4-NO_2Ph	46			**3bb**
4	(*R*)-BINAPHANE	Me	Me	4-NO_2Ph	43		3	**3bb**
5	PBu_3	Me	Me	4-MePh	49			**3cc**
6	PBu_3	Et	Et	Ph	>99			**3dd**
7	(*R*)-BINAPHANE	*c*-Hex	Me	4-ClPh	61	54:46	31/3	**3ee**
8	(*R*)-BINAPHANE	*c*-Hex	Me	4-NO_2Ph	64	>99:1	nd	**3ff**

[a]Yield is isolated yield for both diastereomers of **3**. [b]Diastereomeric ratio (dr) determined by GCMS and ^{1}H NMR analysis of crude product.

Scheme 1. Previously Proposed Mechanism of Phosphine-Catalyzed Formal [2 + 2] Cycloaddition Reaction



Scheme 2. Reaction Monitoring by ^{31}P NMR



and diastereoselection (dr >99:1) were observed. In contrast, moderate levels of diastereoselectivity were observed in these reactions when methylphenylketene and ethylphenylketene were used as ketene substrates (entries 1 and 2, Table 3). Moreover, isobutyraldehyde was investigated as an aliphatic aldehyde substrate in reaction with methylphenylketene but the corresponding β-lactone was obtained in low yield (ca. 35%, dr = 96:4) and low enantiomeric excess (7%).

The reaction of dialkylketenes with aromatic aldehydes was also investigated (Table 4). In general, lower levels of enantioselectivity were observed with dialkylketenes than with alkylarylketenes, with a maximum of 31% ee being obtained (entry 7). Great variability in diastereoselectivity was also observed, with optimal diastereoselectivity being observed with a strongly deactivating substituent in comparison to a weakly deactivating substituent on the aromatic ring of the aldehyde (entry 8 vs entry 7). In some cases low reactivity was displayed by BINAPHANE, and so only racemic product could be obtained through the PBu_3-catalyzed reaction variant (entries 5 and 6). Fu's azaferrocene catalytic system performs considerably better (ee up to 91%) with dialkylketenes and provides a practical alternative to the phosphine catalytic system described in this paper.[8]

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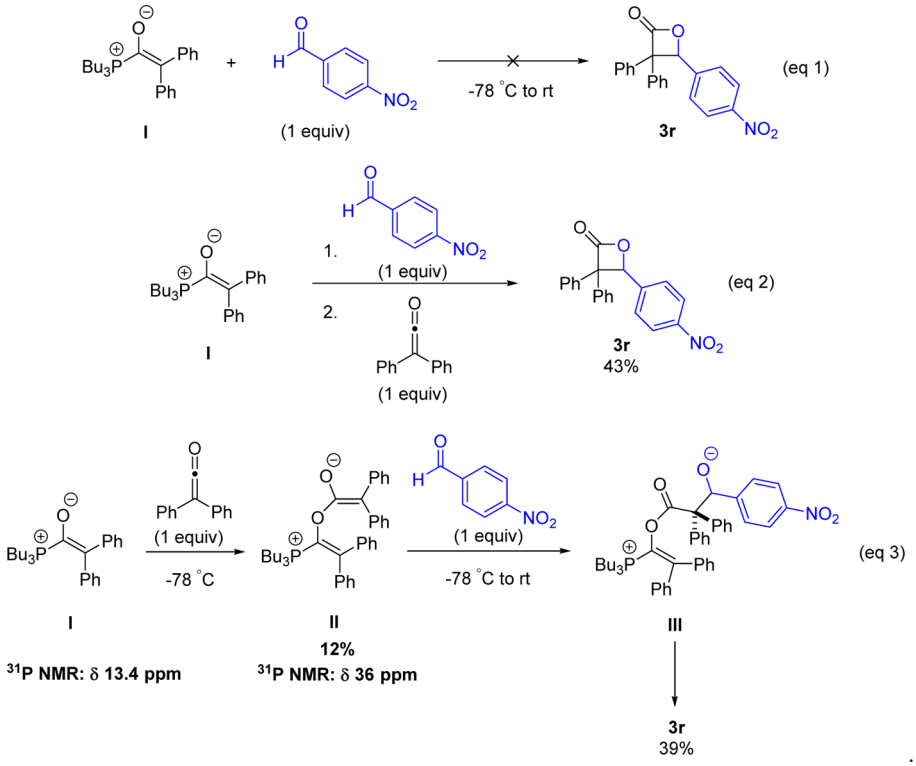
Scheme 3. Reactions of Phosphonium Enolate I



It is important to note that in situ ketene generation (mediated by Hünig's base) for the PBu_3-catalyzed reaction of methylphenylketene with 4-ClPhCHO was attempted but failed. This was in contrast to our recent findings with an alkaloid-catalyzed heterodimerization of ketenes, where two in situ generated ketenes were cross-dimerized.[17] We speculate that this failure is due to stabilization, and hence lowered reactivity, of phosphonium enolate intermediates by a Brönsted acid (Hünig's base salt) or due to reversible protonation of phosphonium enolate intermediates by Hünig's base-derived ammonium salt. Regardless of which process is operative, this has implications for the use of phosphine catalysis for reactions of unstable ketenes. If in situ generated monosubstituted ketenes are required, then the use of an alkaloid catalytic system, which has been demonstrated to be compatible with in situ ketene generation, is recommended.[3,17]

MECHANISM

We originally speculated that the mechanism for formation of *trans*-**3** involved initial attack of the phosphine catalyst on aldehyde **2** to give phosphonium alkoxide **8** (Scheme 1, mechanism A).[13,18] Phosphonium alkoxide **8** would add to another molecule of ketoketene **1** to generate enolate **9**. Intramolecular S_N2 (4-*exo*-tet) would provide *trans*-**3** as the major product.[13] However, in light of our subsequent studies on the phosphine-catalyzed homodimerization of ketoketenes, where we showed that the reaction involved phosphonium enolate intermediates, and recent studies described herein, we have reevaluated the reaction mechanism of the phosphine-catalyzed cycloaddition of ketenes with aldehydes.[19]

Careful ^{31}P NMR monitoring at room temperature (and at −78 °C) of the PBu_3-catalyzed reaction of diphenylketene with 4-NO_2PhCHO revealed signals at 13.4 ppm (55%), 29.9 ppm (2%), and 36.0 ppm (31%) (Scheme 2, eq 1). During our previous studies on the PBu_3-catalyzed homodimerization of diphenylketene we characterized the product of the reaction of PBu_3 and diphenylketene and determined that it had the structure of phosphonium enolate **I** (Scheme 2, eq 2).[19] Phosphonium enolate **I**, generated through reaction of 1 equiv of PBu_3 with 1 equiv of diphenylketene, gave rise to a signal at 13.4 ppm in the ^{31}P NMR spectrum, and from this we deduced that the signal observed at 13.4 ppm in the PBu_3-catalyzed reaction of diphenylketene with 4-NO_2PhCHO was due to phosphonium enolate **I** (Scheme 2, eq 2).[19] We speculate that the signal observed at 29.9 ppm (2%) is due to the aldehyde-derived phosphonium adduct (**9**; Scheme 1) or due to an acylphosphonium intermediate derived from phosphonium enolate **I** (Scheme 2), as acylphosphonium species are known to give signals in the 28−32 ppm range of the ^{31}P NMR spectrum.[18−21]

To investigate whether phosphonium enolate **I** could undergo an aldol-type reaction with an aldehyde to form *β*-lactone **3r**, we subjected a stoichiometric amount of phosphonium enolate **I** to reaction with 4-NO_2PhCHO (Scheme 3, eq 1). Under these conditions, no *β*-lactone (**3r**) was formed (Scheme 3, eq 1). This was in contrast to the result of the phosphine-*catalyzed* reaction (Table 2, entry 18 and Scheme 2, eq 1). Interestingly, when another 1 equiv of diphenylketene was added to the former reaction (that is, added to eq 1 of Scheme 3, after 1 equiv of 4-NO_2PhCHO had been previously added), *β*-lactone **3r** was formed in a yield of 43%. From these results, we inferred that a more complex mechanism than had initially been conceived was responsible for the formation of *β*-lactones.[13]

In an attempt to mimic the formation of intermediates in the reaction, the reaction was also run with 4-NO_2PhCHO added subsequent to the reaction of 1 equiv of phosphonium enolate **I** with 1 equiv of diphenylketene (Scheme 3, eq 3). In this

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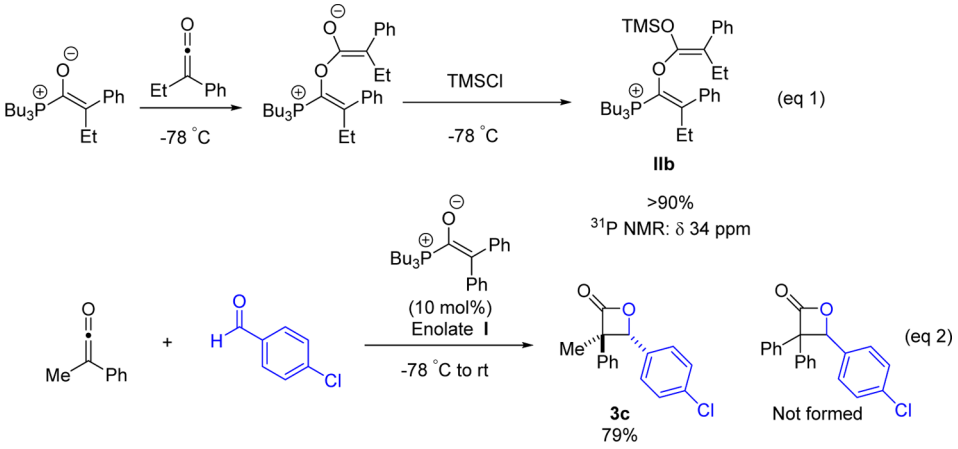
Scheme 4. Additional Mechanistic Experiments

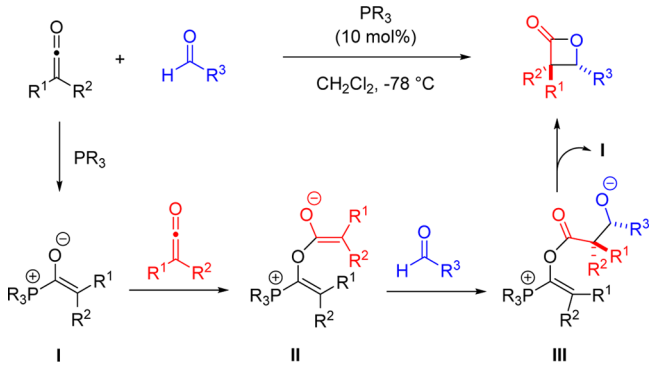


iteration of the reaction, a total of 2 equiv of diphenylketene was added sequentially, 20 min apart, and finally 4-NO_2PhCHO was added, during which time the reaction was continuously monitored by ^{31}P NMR spectroscopy. Ultimately, under these reaction conditions, **3r** was formed in a yield of 39% (Scheme 3, eq 3). After the reaction of PBu_3 with 2 equiv of diphenylketene, a significant new signal was formed at 36 ppm (12% of all P species). Given that *C*-acylation of phosphonium enolate **I** would give an acylphosphonium species, which are known to appear in the range 28−32 ppm, we favor *O*-acylation instead and have assigned structure **II** to the intermediate at 36 ppm.[19−21]

Further support for this assignment was obtained from our phosphine-catalyzed homodimerization studies,[19] where an analogous phosphonium intermediate **IIb** derived from ethylphenylketene was isolated and characterized after trapping with TMSCl (Scheme 4, eq 1); **IIb** gave a signal at 34 ppm in the ^{31}P NMR spectrum which, given the close proximity of the resonance signal of **II**, strongly suggests that **II** resembles it structurally.[20,21] Finally, when a catalytic amount of preprepared phosphonium enolate **I** (derived from diphenylketene and PBu_3) was used as a catalyst for the reaction of methylphenylketene with 4-ClPhCHO, the desired *β*-lactone was formed in a yield of 79% (Scheme 4, eq 2), clearly implicating phosphonium enolate **I** as a catalyst for this and possibly for other phosphine-catalyzed [2 + 2] formal cycloadditions.[13,14,19] All of these ^{31}P NMR monitoring experiments were repeated with ethylphenylketene as the ketene component (instead of diphenylketene), and similar results were observed. This mechanism of catalysis may be operative in other Lewis base catalytic systems, such as N-heterocyclic carbenes.[22] Indeed, Delaude and co-workers have recently demonstrated that enolates derived from ketenes and N-heterocyclic carbenes are important intermediates in NHC-catalyzed *β*-lactam formation.[22]

On the basis of the results of reaction monitoring and control experiments (Schemes 2−4) we propose the following revised mechanism (Scheme 5). Stereoselective addition of the phosphine catalyst to the ketene would afford phosphonium enolate **I**, which acts as the true catalyst (and resting state of the catalyst) in the catalytic cycle.[23] Enolate **I** then undergoes *O*-acylation by reaction with another molecule of the ketene to give phosphonium enolate **II** in a stereoselective fashion.[23] Phosphonium enolate **II** adds to the aldehyde to generate aldolate **III**, which subsequently undergoes cyclization to give a

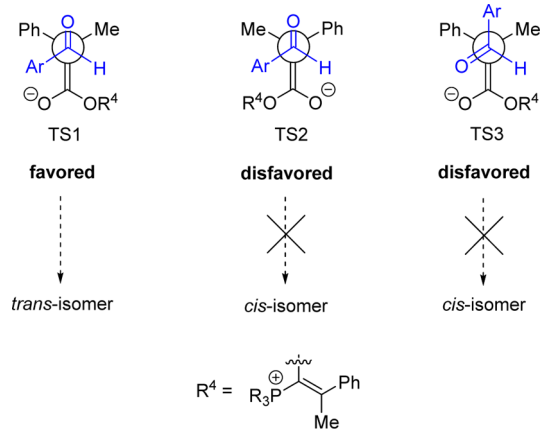
Scheme 5. Proposed Mechanism for Phosphine-Catalyzed Formal [2 + 2] Cycloaddition Reaction



β-lactone product, along with regeneration of the phosphonium enolate **I**.

The preference of the reaction for the trans diastereomer can be rationalized by invoking an anti-periplanar transition state (rather than a gauche transition state) in the reaction between phosphonium enolate **II** and the aldehyde (**II** to **III**, as depicted in Scheme 5, and Scheme 6).[7,13] In the anti-periplanar **TS1**, where steric interactions between the two large substituents (Ar and OR^4) and dipole−dipole repulsions (C−O and C═O) are

Scheme 6. Model for Diastereoselection in Phosphine-Catalyzed Formal [2 + 2] Cycloaddition Reactions



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minimized, formation of the trans diastereomer would be predicted (Scheme 6).[7]

CONCLUSION

In summary, we have developed a versatile phosphine-catalyzed asymmetric reaction of ketenes (alkylaryl and dialkyl) with achiral aldehydes (aromatic and aliphatic) that provides access to β-lactones bearing two stereogenic centers with excellent enantioselectivity (≥85% ee for 10 examples) and good diastereoselectivity (≥90:10 for 13 examples) in many cases. A purely diastereoselective variant of the reaction employing PBu_3 as the nucleophilic catalyst promoted the formation of racemic β-lactones bearing two stereogenic centers with moderate to excellent diastereoselectivity. An analysis of the possible reaction pathways, supported by ^{31}P NMR analysis of reactions and intermediate trapping studies, suggests that the reaction involves phosphonium enolate intermediates, with one of these acting as the true catalyst of the reaction. Current studies involve an exploration of the substrate scope with respect to chiral aldehydes, while future studies will focus on elucidating a model for enantioselection.

EXPERIMENTAL SECTION

General Considerations. THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use. *N,N*-Dimethylethylamine was distilled from calcium hydride under nitrogen.[24] Dichloromethane and diethyl ether were dried by passing through activated alumina columns on a solvent purification system. Tri-*n*-butylphosphine, (*R*)-BINAPHANE, lithium iodide, isobutyraldehyde, benzaldehyde, 4-methylbenzaldehyde, 2-fluorobenzaldehyde, 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, pentanal, hydrocinnamaldehyde, cinnamaldehyde, 3-thiophenecarboxaldehyde, and potassium hydroxide were purchased and distilled in some cases.[24] Iatrobeads (60 μM particle size) and TLC plates (UV254, 250 μM) were used as received. Methylphenylketene, ethylphenylketene, *n*-butylphenylketene, cyclohexylmethylketene, methyl-4-tolylketene, methyl-2-tolylketene, diphenylketene, and ethyl-*N*-methylindolylketene were prepared through amine-mediated dehydrohalogenation. Dimethylketene and diethylketene were prepared through zinc-mediated dehalogenation of the appropriate α-bromoacyl bromide precursor.[25−27]

NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^1H 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) at Oakland University, or from the College of Sciences Major Instrumentation Cluster at Old Dominion University. Low-resolution mass spectra were recorded on a GC/MS instrument with a mass-selective detector and using a Restek Rtx-CL Pesticides2 GC column (30 m, 0.25 mm i.d.). Optical rotations were measured on an automatic polarimeter. IR spectra were recorded on an IR spectrometer.

Analytical high-performance liquid chromatography (HPLC) was performed using an AD column (0.46 cm × 25 cm), an OD-H column (0.46 cm × 25 cm), or an AS-H column (0.46 cm × 25 cm) on an HPLC instrument attached with a diode array detector (deuterium lamp, 190−600 nm) with HPLC-grade isopropyl alcohol and hexanes as the eluting solvents.

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 pure samples for full characterization. Diastereomeric ratios were determined for the crude β-lactones **3** by integrating the tertiary C*H* resonances on the β-lactones in ^1H NMR spectra or by integration of peaks in GC-MS spectra. Enantiomeric excesses were determined by assaying the β-lactones **3** using chiral HPLC analysis (at λ 225 or 254 nm; details given for each compound). Authentic racemic samples for chiral HPLC analysis were generated through the PBu_3-catalyzed reaction. Compounds **3a−d,i,j,l−o,q,r,u,v** were prepared and characterized (as their carboxylic derivatives in many cases) as previously described by our group.[13] Tributyl[2-phenyl-1-(2-phenyl-1-trimethylsilanyloxy-but-1-enyloxy)-but-1-enyl]phosphonium (**IIb**) (Scheme 4, eq 1) was prepared and characterized as previously described.[19]

Procedure A for β-Lactone Synthesis. To a stirred solution of aldehyde (1 equiv or multiple equivalents) and phosphine catalyst (PBu_3 or BINAPHANE) (0.1 equiv) in dichloromethane (amount specified for each example), at −78 °C under a nitrogen atmosphere, was added a solution of disubstituted ketene (1 equiv) in dichloromethane (amount specified for each example) over a period of 4 h using a syringe pump. The reaction solution was stirred at −78 °C for another 4 h. The reaction solution was then warmed to room temperature gradually over 4−12 h in the cooling bath (total reaction time 12−20 h). The crude solution was passed through a plug column (Iatrobeads, 2.5 × 3.0 cm, 6 g) (50 × weight of product mixture). The plug column was eluted with an EtOAc/hexane solvent system (100−250 mL), and the solvent was removed under vacuum to furnish the desired β-lactone **3** in high purity as determined by ^1H NMR and GC-MS analysis.

Procedure B for β-Lactone Synthesis. To a stirred solution of aldehyde (1 equiv) and phosphine catalyst (PBu_3 or BINAPHANE) (0.1 equiv) in THF (amount specified for each example), at −78 °C under a nitrogen atmosphere, was added a solution of disubstituted ketene (3 equiv) in THF (amount specified for each example) in one portion. The reaction solution was stirred at −78 °C for another 8 h. The reaction solution was then warmed to room temperature gradually over 12 h in the cooling bath (total reaction time 20 h). Purification was as for procedure A.

Procedure for β-Hydroxy Acid Synthesis (from 3b−d,j−3o,u,3v).[13] The following procedure was used to facilitate purification and characterization of those β-lactones not obtained in high purity (>95%) through use of procedure A or B. A stirred mixture of crude β-lactone **3** (0.30 mmol, 1.0 equiv) and aqueous KOH (1.0 N; 0.60 mL, 0.60 mmol, 2.0 equiv) in THF (1.2 mL) was heated to 60 °C in a sealed tube for 6−12 h. After it was cooled, the reaction mixture was diluted with water (2 mL) and extracted with dichloromethane (30 mL) to remove undesired product. The aqueous layer was acidified with HCl (10%) and extracted with dichloromethane (20 mL × 3), and the combined extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent under vacuum followed by column chromatographic purification using a hexane/EtOAc solvent system furnished the desired β-hydroxy acid **7**. Isolated yields were determined for two steps from the relevant disubstituted ketene.[13]

*(±)-3-Methyl-4-(2-nitrophenyl)-3-phenyloxetan-2-one (**3e**).* Following procedure A, methylphenylketene (31 mg, 0.23 mmol) in CH_2Cl_2 (0.4 mL) was added to 2-nitrobenzaldehyde (35 mg, 0.23 mmol) and *n*-Bu_3P (5 mg, 0.025 mmol) in CH_2Cl_2 (0.2 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3e** as a white solid (23 mg, 35% yield): dr = 69:31 (by GC-MS); IR (CH_2Cl_2) 2977, 2924, 1832, 1526, 1347, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 8.27 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.58−7.53 (m, 2H), 7.53−7.46 (m, 2H), 7.45−7.39 (m, 1H), 6.16 (s, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 173.1, 146.9, 137.7, 135.0, 132.5, 130.0, 129.2, 128.6, 128.5, 126.2, 125.6, 82.1, 66.0, 15.6; $(M + H)^+$ HRMS *m*/*z* calcd for $(C_{16}H_{14}NO_4)^+$ 284.0923, found 284.0924.

*(±)-4-(2-Fluorophenyl)-3-methyl-3-phenyloxetan-2-one (**3f**).* Following procedure A, methylphenylketene (31 mg, 0.23 mmol) in CH_2Cl_2 (0.3 mL) was added to 2-fluorobenzaldehyde (29 mg, 0.23 mmol) and *n*-Bu_3P (5 mg, 0.025 mmol) in CH_2Cl_2 (0.2 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3f** as a colorless gel-like liquid (33 mg, 56% yield): dr = 65:35 (by ^1H NMR); IR (CH_2Cl_2) 3064, 2976, 2930, 1830, 1234, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.52−7.29 (m, 3H), 7.24−7.07 (m, 3H), 6.98−6.86 (m, 1H), 5.98 (s, 1H), 1.33 (s, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$, major diastereomer) δ 172.6, 159.9 (d, J = 244.1 Hz), 139.5, 135.7, 130.6 (d, J = 8.1 Hz), 129.3, 128.2, 127.5 (d, J = 3.7 Hz), 126.4, 125.9 (d, J = 3.4 Hz), 115.6 (d, J = 20.4 Hz), 78.4 (d, J = 3.6 Hz), 65.3, 20.3; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{14}O_2F)^+$ 257.0978, found 257.0969.

(±)-4-(2-Chlorophenyl)-3-methyl-3-phenyloxetan-2-one (**3g**). Following procedure A, methylphenylketene (31 mg, 0.23 mmol) in CH_2Cl_2 (0.3 mL) was added to 2-chlorobenzaldehyde (33 mg, 0.23 mmol) and n-Bu_3P (5 mg, 0.025 mmol) in CH_2Cl_2 (0.2 mL). Elution with 1%, 2%, and then 5% EtOAc/hexane through a plug column of neutral silica gel afforded **3g** as a white solid (25 mg, 39% yield): dr = 62:38 (by ^1H NMR); IR (CH_2Cl_2) 2977, 2930, 1833, 1216, 1135, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major isomer) δ 7.68−7.59 (m, 1H), 7.52−7.35 (m, 3H), 7.26−7.19 (m, 1H), 7.19−7.06 (m, 4H), 5.95 (s, 1H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 173.0, 138.5, 135.3, 133.7, 131.9, 129.9, 129.2, 128.5, 127.6, 126.9, 126.6, 81.8, 67.0, 23.1; $(M + H)^+$ HRMS m/z calcd $(C_{16}H_{14}O_2Cl)^+$ 273.0682, found 273.0680.

(±)-4-(3-Chlorophenyl)-3-methyl-3-phenyloxetan-2-one (**3h**). Following procedure A, methylphenylketene (34 mg, 0.26 mmol) in CH_2Cl_2 (0.4 mL) was added to 3-chlorobenzaldehyde (33 mg, 0.23 mmol) and n-Bu_3P (5 mg, 0.025 mmol) in CH_2Cl_2 (0.3 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3h** as a colorless gel-like liquid (34 mg, 49% yield): dr >99:1 (by ^1H NMR); IR (CH_2Cl_2) 3064, 2976, 2929, 1830, 1261, 1137, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.51−7.46 (m, 4H), 7.46−7.38 (m, 4H), 7.36−7.31 (m, 1H), 5.71 (s, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.4, 137.2, 135.4, 130.5, 129.6, 129.2, 128.4, 125.9, 125.7, 123.9, 82.1, 65.0, 20.5; $(M + H)^+$ HRMS m/z calcd $(C_{16}H_{14}O_2Cl)^+$ 273.0682, found 273.0682.

(3R,4R)-3-Butyl-4-(4-chlorophenyl)-3-phenyloxetan-2-one (**3k**). Following procedure A, n-butylphenylketene (62 mg, 0.36 mmol) in CH_2Cl_2 (0.6 mL) was added to 4-chlorobenzaldehyde (50 mg, 0.36 mmol) and (*R*)-BINAPHANE (24 mg, 0.034 mmol) in CH_2Cl_2 (0.3 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3k** as a gel-like liquid (64 mg, 58% yield): dr = 92:8 (by ^1H NMR); HPLC analysis 41% ee (major diastereomer), >99% ee (minor diastereomer) (Daicel Chiralpak AS-H column; 0.5 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 14.7 and 21.3 min (major diastereomer), 18.4 and 23.4 min (minor diastereomer)); IR (CH_2Cl_2) 2957, 2936, 2871, 1825, 1114, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 7.54−7.36 (m, 9H), 5.66 (s, 1H), 1.71−1.59 (m, 1H), 1.52−1.40 (m, 1H), 1.39−1.19 (m, 2H), 1.15−0.75 (m, 2H), 0.67 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 171.9, 138.0, 135.0, 133.5, 129.3, 129.3, 128.1, 127.4, 126.4, 82.4, 68.4, 33.8, 26.1, 22.8, 13.8; $(M + H)^+$ HRMS m/z calcd $(C_{19}H_{20}O_2Cl)^+$ 315.1152, found 315.1144.

(±)-4-(3-Chlorophenyl)-3-methyl-3-p-tolyloxetan-2-one (**3p**). Following procedure A, methyl-4-tolylketene (31 mg, 0.23 mmol) in CH_2Cl_2 (0.4 mL) was added to 3-chlorobenzaldehyde (33 mg, 0.23 mmol) and n-Bu_3P (5 mg, 0.025 mmol) in CH_2Cl_2 (0.2 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3p** as a colorless liquid (25 mg, 37% yield): dr >99:1 (by ^1H NMR); IR (CH_2Cl_2) 2976, 2927, 1830, 1212, 1137, 1115, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47−7.39 (m, 3H), 7.38−7.26 (m, 5H), 5.68 (s, 1H), 2.41 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 138.2, 137.3, 136.4, 135.3, 130.4, 130.2, 129.2, 125.9, 125.6, 123.9, 82.3, 64.7, 21.3, 20.3; $(M + H)^+$ HRMS m/z calcd $(C_{17}H_{16}O_2Cl)^+$ 287.0839, found 287.0837.

(3R,4R)-4-Butyl-3-methyl-3-phenyloxetan-2-one (**3s**). Following procedure A, methylphenylketene (53 mg, 0.40 mmol) in CH_2Cl_2 (0.6 mL) was added to pentanal (103 mg, 1.20 mmol) and (*R*)-BINAPHANE (28 mg, 0.040 mmol) in CH_2Cl_2 (0.4 mL). Elution with 5% EtOAc/hexane through a plug column of neutral silica gel afforded **3s** as a colorless liquid (37 mg, 42% yield): dr = 72:28 (by ^1H NMR); IR (CH_2Cl_2) 2958, 2932, 2872, 1820, 1142, 1095, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 7.47−7.27 (m, 5H), 4.67 (dd, J = 8.5, 5.4 Hz, 1H), 2.05−1.86 (m, 2H), 1.64 (s, 3H), 1.54−1.15 (m, 4H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 173.4, 129.3, 128.0, 126.8, 125.7, 83.4, 61.7, 30.5, 28.0, 22.8, 19.2, 14.1; $(M + H)^+$ HRMS m/z calcd $(C_{14}H_{19}O_2)^+$ 219.1385, found 219.1384.

(3R,4R)-4-Butyl-3-ethyl-3-phenyloxetan-2-one (**3t**). Following procedure A, ethylphenylketene (51 mg, 0.35 mmol) in CH_2Cl_2 (0.6 mL) was added to pentanal (90 mg, 1.04 mmol) and (*R*)-BINAPHANE (23 mg, 0.033 mmol) in CH_2Cl_2 (0.3 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3t** as a colorless gel (68 mg, 83% yield): dr = 65:35 (by ^1H NMR); $[\alpha]_D^{24}$ = 61.2° (c = 0.31, CH_2Cl_2); IR (CH_2Cl_2) 2960, 2933, 2873, 1810, 1262, 1117, 1098, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 7.57−7.21 (m, 5H), 4.51 (dd, J = 10.0, 2.8 Hz, 1H), 2.29−2.15 (m, 1H), 2.03−1.87 (m, 1H), 1.55−1.36 (m, 2H), 1.36−1.19 (m, 3H), 1.06−0.91 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 172.8, 128.9, 127.9, 127.1, 126.5, 82.9, 67.5, 32.4, 30.8, 27.7, 22.5, 14.0, 9.2; $(M + H)^+$ HRMS m/z calcd $(C_{15}H_{21}O_2)^+$ 233.1542, found 233.1539.

(R)-3,3-Dimethyl-4-phenyloxetan-2-one (**3aa**).[8] Following procedure B, dimethylketene (36 mg, 0.51 mmol) in THF (1.0 mL) was added to benzaldehyde (18 mg, 0.17 mmol) and (*R*)-BINAPHANE (12 mg, 0.017 mmol) in THF (0.8 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3aa** as a colorless liquid (14 mg, 47% yield): HPLC analysis 22% ee (Daicel Chiralpak AS-H column; 1.0 mL/min; solvent system 10% isopropyl alcohol in hexane; retention time 5.7 min (major), 6.3 min (minor)); $[\alpha]_D^{24}$ = 2.5° (c = 0.08, CH_2Cl_2); IR (CH_2Cl_2): 2974, 2934, 1827, 1183, 1101, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.48−7.35 (m, 4H), 7.33−7.29 (m, 1H), 5.34 (s, 1H), 1.61 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 135.6, 128.9, 128.7, 125.4, 83.1, 57.0, 22.8, 18.2; $(M + H)^+$ HRMS m/z calcd for $(C_{11}H_{13}O_2)^+$ 177.0916, found 177.0921.

(R)-3,3-Dimethyl-4-(4-nitrophenyl)oxetan-2-one (**3bb**). Following procedure B, dimethylketene (34 mg, 0.49 mmol) in THF (0.7 mL) was added to 4-nitrobenzaldehyde (24 mg, 0.16 mmol) and (*R*)-BINAPHANE (11 mg, 0.016 mmol) in THF (0.9 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3bb** as a slightly yellow solid (15 mg, 43% yield): HPLC analysis 3% ee (Daicel Chiralpak AD column; 1.0 mL/min; solvent system 10% isopropyl alcohol in hexane; retention time 10.4 min (major), 11.6 min (minor)); IR (CH_2Cl_2) 2972, 2933, 1829, 1521, 1347, 1182, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 8.33 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 5.42 (s, 1H), 1.66 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 148.3, 142.8, 126.4, 124.3, 81.8, 58.0, 22.7, 18.4; $(M + H)^+$ HRMS m/z calcd for $(C_{11}H_{12}NO_4)^+$ 222.0766, found 222.0763.

(±)-3,3-Dimethyl-4-p-tolyloxetan-2-one (**3cc**). Following procedure B, dimethylketene (68 mg, 0.97 mmol) in THF (0.8 mL) was added to 4-methylbenzaldehyde (40 mg, 0.33 mmol) and n-Bu_3P (7 mg, 0.034 mmol) in THF (0.4 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3cc** as a white solid (31 mg, 49% yield); IR (CH_2Cl_2) 2971, 2927, 2873, 1828, 1178, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.24 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 5.31 (s, 1H), 2.39 (s, 3H), 1.59 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 138.6, 132.5, 129.6, 125.4, 83.3, 56.8, 22.7, 21.4, 18.2; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{15}O_2)^+$ 191.1072, found 191.1070.

(±)-3,3-Diethyl-4-phenyloxetan-2-one (**3dd**).[8] Following procedure B, diethylketene (51 mg, 0.52 mmol) in THF (1.2 mL) was added to benzaldehyde (18 mg, 0.17 mmol) and n-Bu_3P (4 mg, 0.020 mmol) in THF (0.6 mL). Elution with 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3dd** as a colorless liquid (35 mg, >99% yield): IR (CH_2Cl_2): 2972, 2943, 1823, 1246, 1146, 1102, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47−7.40 (m, 2H), 7.40−7.34 (m, 1H), 7.34−7.28 (m, 2H), 5.39 (s, 1H), 1.99 (q, J = 7.6 Hz, 2H), 1.50−1.38 (m, 1H), 1.33−1.20 (m, 1H), 1.14 (t, J = 7.5 Hz, 3H), 0.78 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 135.5, 128.7, 128.6, 125.8, 81.0, 64.7, 24.8, 22.0, 8.8, 8.0; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{17}O_2)^+$ 205.1229, found 205.1227.

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*(3R,4R)-4-(4-Chlorophenyl)-3-cyclohexyl-3-methyloxetan-2-one (**3ee**).* Following procedure A, cyclohexylmethylketene (51 mg, 0.37 mmol) in CH_2Cl_2 (0.6 mL) was added to 4-chlorobenzaldehyde (51 mg, 0.36 mmol) and (*R*)-BINAPHANE (24 mg, 0.034 mmol) in CH_2Cl_2 (0.3 mL). Elution with 2.5% EtOAc/hexane through a plug column of neutral silica gel afforded **3ee** as a white solid (62 mg, 61% yield): dr = 54:46 (by ^{1}H NMR); HPLC analysis 31% ee (major diastereomer), 3% ee (minor diastereomer) (Daicel Chiralpak OD-H column; 1.0 mL/min; solvent system: 10% isopropyl alcohol in hexane; retention times 4.1 and 5.3 min (major diastereomer), 4.5 and 4.8 min (minor diastereomer)); IR (CH_2Cl_2) 2928, 2853, 1825, 1267, 1242, 1157, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer) δ 7.41 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 5.21 (s, 1H), 2.03−1.94 (m, 1H), 1.82−1.69 (m, 1H), 1.65−1.55 (m, 2H), 1.53 (s, 3H), 1.49−1.41 (m, 1H), 1.34−1.24 (m, 1H), 1.22−1.09 (m, 2H), 1.09−0.95 (m, 1H), 0.95−0.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ 174.3, 135.0, 133.7, 128.8, 128.4, 83.5, 63.8, 38.2, 27.8, 26.4, 26.3, 26.2, 26.2, 16.3; (M + H)$^+$ HRMS m/z calcd $(C_{16}H_{20}O_2Cl)^+$ 279.1152, found 279.1151.

*(3R,4R)-3-Cyclohexyl-3-methyl-4-(4-nitrophenyl)oxetan-2-one (**3ff**).* Following procedure A, cyclohexylmethylketene (34 mg, 0.25 mmol) in CH_2Cl_2 (0.4 mL) was added to 4-nitrobenzaldehyde (38 mg, 0.25 mmol) and (*R*)-BINAPHANE (16 mg, 0.023 mmol) in CH_2Cl_2 (0.2 mL). Elution with 5% and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded **3ff** as a white solid (47 mg, 64% yield): dr >99:1 (by ^{1}H NMR); $[\alpha]_D^{24}$ = 31.9° (c = 0.80, CH_2Cl_2); IR (CH_2Cl_2) 2932, 2856, 1822, 1516, 1449, 1346, 1159, 1105, 1081 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.30 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 5.50 (s, 1H), 2.10−1.74 (m, 6H), 1.49−1.09 (m, 5H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 148.1, 143.2, 126.6, 124.2, 78.6, 65.7, 42.9, 28.6, 28.1, 26.4, 13.7; (M + H)$^+$ HRMS m/z calcd $(C_{16}H_{20}NO_4)^+$ 290.1392, found 290.1383.

Mechanistic Studies. *Bu_3P-Catalyzed Reaction of Diphenylketene with 4-Nitrobenzaldehyde (Scheme 2, eq 1).* Following procedure A, diphenylketene (98 mg, 0.50 mmol) in CH_2Cl_2 (0.8 mL) was added to 4-nitrobenzaldehyde (76 mg, 0.50 mmol) and Bu_3P (10 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL). After the syringe pump addition of the ketene solution, the reaction mixture was stirred at −78 °C for 1 h. ^{31}P NMR (162 MHz, 85% H_3PO_4) analysis of the reaction solution was then performed: δ 36.0 (31%), 29.9 (2%), 13.4 (55%) ppm. The remaining solution in the reaction flask was treated as per procedure A. 4-(4-Nitrophenyl)-3,3-diphenyloxetan-2-one (**3r**) was obtained as a yellowish solid (68 mg, 73%). Characterization data for isolated **3r** agreed with those previously reported by us.[13]

*Quantitative Generation of Phosphonium Enolate **I** from Diphenylketene (Scheme 2, eq 2).*[19] To diphenylketene **1r** (109 mg, 0.56 mmol, l equiv) in CH_2Cl_2 (1.2 mL, 0.5 M) was added Bu_3P (0.14 mL, 0.56 mmol, 1 equiv) dropwise over 5 min at −78 °C, and the resulting solution was stirred at −78 °C for 20 min. ^{31}P NMR analysis of the solution (at room temperature and at −78 °C) indicated the formation of phosphonium enolate **I** with >98% purity: ^{31}P NMR (162 MHz, 85% H_3PO_4) δ 35.9 (1%), 13.4 (99%) ppm.[19]

*Attempted Reaction of Phosphonium Enolate **I** with 4-Nitrobenzaldehyde (Scheme 3, eq 1).* To diphenylketene **1r** (132 mg, 0.68 mmol, l equiv) in CH_2Cl_2 (0.9 mL, 0.7 M) was added Bu_3P (0.17 mL, 0.68 mmol, 1 equiv) dropwise over 5 min at −78 °C, and the resulting phosphonium enolate solution was stirred at −78 °C for 20 min. 4-Nitrobenzaldehyde (103 mg, 0.68 mmol) in CH_2Cl_2 (0.8 mL) was added to the phosphonium enolate solution, and the mixture was stirred at −78 °C for 3.5 h. The reaction solution was warmed slowly to room temperature overnight. GC-MS analysis of the reaction solution confirmed that **3r** was not formed.

*Sequential Reaction of Phosphonium Enolate **I** with 4-Nitrobenzaldehyde and Diphenylketene (Scheme 3, eq 2).* To diphenylketene **1r** (125 mg, 0.64 mmol, l equiv) in CH_2Cl_2 (0.7 mL, 0.9 M) was added Bu_3P (0.16 mL, 0.64 mmol, 1 equiv) dropwise over 5 min at −78 °C, and the resulting phosphonium enolate solution was stirred at −78 °C for 20 min. 4-Nitrobenzaldehyde (97 mg, 0.64 mmol) in CH_2Cl_2 (0.4 mL) was added to the phosphonium enolate solution, and the reaction solution was stirred at −78 °C for 3.5 h. ^{31}P NMR (162 MHz, 85% H_3PO_4) analysis of the reaction solution: δ 46.8 (19%), 37.7 (9%), 35.4 (4%), 13.5 (53%), −31.1 (16%) ppm. Then diphenylketene (125 mg, 0.64 mmol, l equiv) in CH_2Cl_2 (0.5 mL) was added to the reaction solution. The reaction solution was warmed slowly to room temperature overnight. **3r** was obtained as a yellowish solid (95 mg, 43%). Characterization data for isolated **3r** agreed with those previously reported by us.[13]

*Sequential Reaction of Phosphonium Enolate **I** with Diphenylketene and 4-Nitrobenzaldehyde (Scheme 3, eq 3).* To diphenylketene **1r** (115 mg, 0.59 mmol, l equiv) in CH_2Cl_2 (0.5 mL, 1.2 M) was added Bu_3P (0.15 mL, 0.59 mmol, 1 equiv) dropwise over 5 min at −78 °C, and the resulting phosphonium enolate solution was stirred at −78 °C for 20 min. ^{31}P NMR (162 MHz, 85% H_3PO_4) analysis of the reaction solution: δ 35.9 (3%), 13.4 (83%), −31.0 (13%) ppm. Diphenylketene (122 mg, 0.64 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL) was added to the phosphonium enolate solution, and the mixture was stirred at −78 °C for 3.5 h. ^{31}P NMR (162 MHz, 85% H_3PO_4) analysis of the reaction solution: δ 13.4 (87%), 36.1(12%) ppm. After the solution was stirred at −78 °C for 25 min, 4-nitrobenzaldehyde (90 mg, 0.60 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) was added to the phosphonium enolate solution. The reaction solution was warmed slowly to room temperature overnight. **3r** was obtained as a yellowish solid (80 mg, 39%). Characterization data for isolated **3r** agreed with those previously reported by us.[13]

*Phosphonium Enolate **I** Catalyzed Reaction of Methylphenylketene with 4-Chlorobenzaldehyde (Scheme 4, eq 2).* Following procedure A, methylphenylketene (59 mg, 0.45 mmol) was added to 4-chlorobenzaldehyde (62 mg, 0.44 mmol) and phosphonium enolate **I** (94 μL, 0.044 mmol, 0.47 M solution in CH_2Cl_2). **3c** was obtained as a white solid (95 mg, 79%): dr = 97:3 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.52−7.45 (m, 6H), 7.43−7.37 (m, 3H), 5.72 (s, 1H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 139.5, 134.9, 133.6, 129.5, 129.3, 128.3, 127.1, 125.6, 82.3, 64.8, 20.4; (M + H)$^+$ HRMS m/z calcd $(C_{16}H_{14}O_2Cl)$ 273.0682, found 273.0675.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra and HPLC chromatograms for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729−744. (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4−5. (c) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998**, 1655−1661. (d) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230−6231.

(2) (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412−10422. (b) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470−10471. (c) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654−13655. (d) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438−7439. (e) Wang, Y.; Tennyson, R.; Romo, D. *Heterocycles* **2004**, *64*, 605−658.

(3) (a) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771−6803. (b) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 744−746. (d) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434. (e) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14−15. (f) Kull, T.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5461−5464.
(4) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979. (c) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87−130.
(5) (a) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252. (b) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946.
(6) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352−5353.
(7) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809−1812.
(8) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358−6360.
(9) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101−8103.
(10) Douglas, J.; Taylor, J. E.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2013**, *78*, 3925−3938.
(11) (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827−1836. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035−1050. (c) Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473−3477.
(12) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234−12235.
(13) Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2010**, *12*, 1664−1667.
(14) (a) Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777−1780. (b) Ibrahim, A. A.; Wei, P.-H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901−7904. (c) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784−1787.
(15) (a) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499−1505. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426−1429.
(16) The absolute configuration of **3r** (entry 18, Table 2) was determined to be *R*, through X-ray crystallographic analysis (see ref 13 for further details). The absolute configuration of most *β*-lactones **3a**−**3ff** was assigned to be *R*,*R* by analogy.
(17) Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. *J. Am. Chem. Soc.* **2012**, *134*, 2942−2945.
(18) Lee, S. W.; Trogler, W. C. *J. Org. Chem.* **1990**, *55*, 2644−2648.
(19) Wei, P.-H.; Ibrahim, A. A.; Mondal, M.; Nalla, D.; Harzmann, G. D.; Tedeschi, F. A.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2010**, *51*, 6690−6694.
(20) (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359. (b) Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* **2003**, *44*, 4411−4413. (c) Zhu, X.-F.; Henry, C. E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722−6723.
(21) (a) Hudson, H. R.; Dillon, K. B.; Walker, B. J. ^{31}P NMR Data of Four Coordinate Phosphonium Salts and Betaines.In *Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press: Boca Raton, FL, 1991; pp 181−226. (b) Dennis, L. W.; Bartuska, V. J.; Maciel, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 230−235. (c) Chestnut, D. B.; Quin, L. D. *Tetrahedron* **2005**, *61*, 12343−12349.
(22) (a) Hans, M.; Wouters, J.; Demonceau, A.; Delaude, L. *Chem. Eur. J.* **2013**, *19*, 9668−9676. (b) Maji, B.; Mayr, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 11163−11167. (c) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108−1113. (d) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277−280.
(23) (a) Cannizzaro, C. E.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 2668−2669. (b) Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 10992−11008.
(24) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, U.K., 2002.
(25) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007.
(26) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176−6177.
(27) Allen, A. D.; Baigrie, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138−145.