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Diastereoselective Reaction of Sulfoxonium Ylides, Aldehydes and Ketenes: An Approach to *trans*-γ-Lactones

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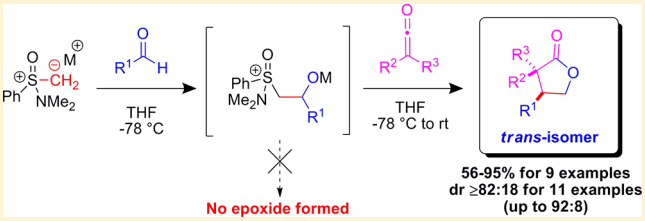
Supporting Information

ABSTRACT: In this paper, a novel approach to γ-lactones from the reaction of sulfoxonium ylides, aldehydes, and ketenes is described. The new ylide-based method provides access to γ-lactones from disubstituted ketenes, in good yields, and with good diastereoselectivity favoring the *trans*-diastereomer (11 examples with dr ≥ 82:18, dr up to 92:8).



γ-Lactones are structural elements that are found as part of many natural products (in about 10% of all natural products), including the paraconic acids, and numerous bicyclic and tricyclic ring systems (e.g., xanthatin).[1] γ-Lactones have a range of biological activity including strong antifungal, antibiotic, antitumor, antiviral, and anti-inflammatory activity, which underscores their potential for pharmaceutical development.[1,2] γ-Lactones have also been used as building blocks for the synthesis of complex molecules.[3] Both intramoleular and intermolecular approaches to the γ-lactone scaffold have been investigated.[4−6] Methods for the synthesis of γ-lactones are often characterized by multistep approaches, limited substrate scope, modest diastereoselectivity or enantioselectivity, and/or the involvement of expensive reagents for the synthesis of enantioenriched γ-lactones.[1−6] Among the best direct (one-pot) *intermolecular* methods are the contributions of Fukuzawa and Procter involving ephedrinyl chiral auxiliary controlled-SmI_2 reductive coupling of aldehydes and acrylates in solution- and solid-phase approaches to *cis*-γ-lactones, albeit with 2−5 equiv of SmI_2 required for complete conversion.[4a,b] *N*-Heterocyclic carbenes (NHC) have also been used as organocatalysts for the construction of *cis*-γ-lactones, although this has been one of the less developed NHC-catalyzed processes with respect to asymmetric induction and substrate scope.[4,7] In recent years, transition-metal catalysis has been applied to the stereoselective synthesis of γ-lactones, but this approach, with few exceptions, has been limited to the *intramolecular* construction of γ-lactones, is predicated on the use of expensive catalysts, and often requires many synthetic steps to assemble the substrates for such cyclization reactions (e.g., four steps or more).[4,8] In this paper, we describe a versatile and novel strategy for providing access to this important class of cyclic molecules, which overcomes many of the deficiencies described with previous systems.

In the 1960s, A. W. Johnson's group and Corey's group introduced and developed the reaction of sulfonium and sulfoxonium ylides with aldehydes that provided an important route to epoxides, and subsequently became known as the Johnson−Corey−Chaykovsky reaction.[9] The synthesis of epoxides through the reaction of aminosulfoxonium ylides with aldehydes was later developed by C. R. Johnson.[9d,e] The latter reaction was proposed to involve a betaine intermediate, formed reversibly as part of a stepwise mechanism.[10,11]

While limited studies have been carried out investigating the reaction of betaines, derived from aziridines, with cumulenes such as carbon disulfide under harsh reaction conditions (refluxing CH_3CN or *t*-BuOH), it is quite striking that no work has been carried out exploring the reactivity of in situ generated betaines with ketenes.[12] As part of our research program on the development of new synthetic reaction methodologies involving ketenes, we began work on the development of a reaction of onium ylides, aldehydes, and ketenes that we anticipated would provide access to γ-lactones.[13,14] We proposed that, by carrying out betaine generation from the reaction of sulfoxonium ylide **2a** (derived from sulfoxonium salt **1a**) and aldehyde **3** under mild conditions (at −78 °C), cyclization to give epoxide (Johnson−Corey−Chaykovsky reaction) would be slowed (Scheme 1). We anticipated that the betaine intermediate **A** could be intercepted by a ketene **4** to generate an enolate **B** at low temperature. The enolate intermediate **B** would then be expected to undergo 5-*exo-tet* cyclization to generate the 3,5-disubstituted γ-lactone product **C**, with concomitant loss of the sulfinamide leaving group X (Scheme 1).

In preliminary studies, we determined that chiral amino-sulfoxonium ylide **2a**, obtained through treatment of salt **1a** with base, was superior to all other onium ylides for γ-lactone formation (under Table 1 conditions).[15] In all cases,

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Scheme 1. Proposal for New Route to γ-Lactones

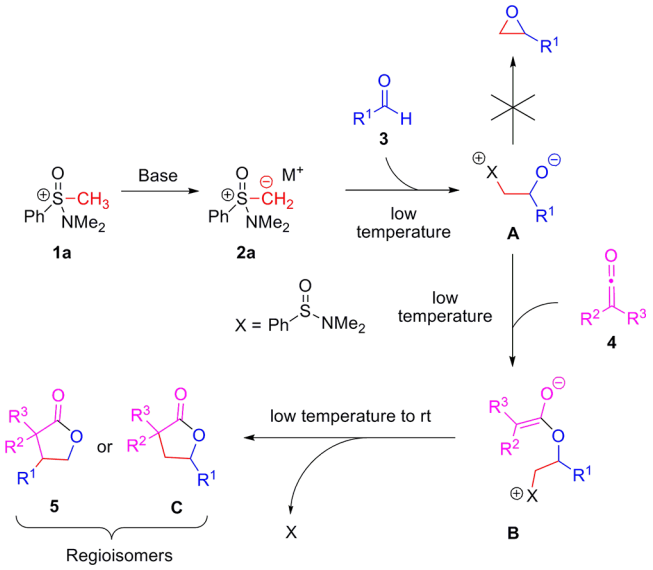
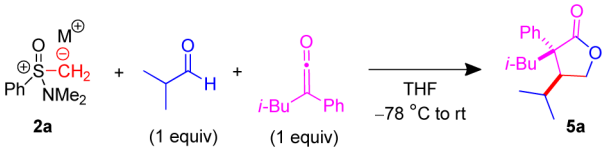


Table 1. Optimization of the Diastereoselective Synthesis of γ-Lactones

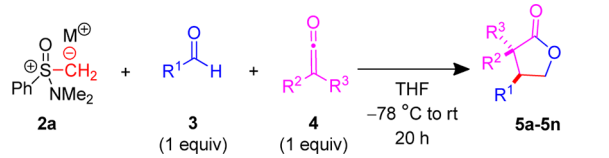


entry	base (metal salt additive)	M^+	metal salt (equiv)	% yield[a]	dr[b]
1	NaHMDS	Na		15	88:12
2	KHMDS	K		trace	
3	*n*-BuLi	Li		32	88:12
4	*n*-BuLi	Li (50 °C)[c]		61	79:21
5	*n*-BuLi ($ZnCl_2$)	ZnCl	1	45	70:30
6	*n*-BuLi ($MgCl_2$)	MgCl	1	77	86:14
7	*n*-BuLi ($MgCl_2$)	MgCl	2	93	88:12
8	*n*-BuLi ($MgCl_2$)	MgCl (50 °C)[c]	1	95	85:15
9	*n*-BuLi ($MgBr_2$)	MgBr	1	30	86:14
10	*n*-BuLi (MgI_2)	MgI	1	56	86:14
11	*n*-BuLi ($AlCl_3$)	$AlCl_2$	1	60	64:36
12	*n*-BuLi (CuI)	Cu	1	79	74:26

[a]Percent yield is the isolated yield for **5**. [b]Diastereomeric ratio (dr) determined by GCMS and ^{1}H NMR analysis of crudes. [c]heated at 50 °C for 15 min after ketene addition.

tetrafluoroborate (BF_4^-) was used as a non-nucleophilic counterion for sulfoxonium salt **1a**/ylide **2a** in order to minimize side reactions with ketenes (e.g., with iodide as a counterion). For all entries in Table 1, the aldehyde was added slowly to the ylide **2a** at −78 °C, and then the ketene was added slowly over 60 min at −78 °C to the reaction solution. The reaction was allowed to warm to room temperature overnight in most cases. Carrying out ketene addition at a higher temperature (e.g., −30 °C) led to poor conversion to γ-lactone (<20%). The use of bases other than *n*-BuLi led to poorer yields of lactone **5a** (Table 1, entry 1−3). A variety of metal salt additives were investigated in an effort to elevate the yield of **5a** without decreasing diastereoselectivity (Table 1, entry 5−12). Best results were obtained with $MgCl_2$ (entries 6−8). We speculate that the additive $MgCl_2$ has a number of roles in our reaction system. Primarily, it activates aliphatic aldehydes, such as isobutyraldehyde, to undergo reaction with the sulfoxonium ylide **2a**. More reactive aromatic aldehydes (entries 2−10, Table 2) do not need this additive to enable

Table 2. Substrate Scope of the Diastereoselective Synthesis of γ-Lactones



entry	R^1	R^2	R^3	% yield[a]	dr[b]	lactone[c]
1	*i*-Pr	*i*-Bu	Ph	93	88:12	**5a**
2	Ph	*i*-Bu	Ph	60	83:17	**5b**
3	2-NO_2Ph	*i*-Bu	Ph	70	87:13	**5c**
4	2-ClPh	*i*-Bu	Ph	43	83:17	**5d**
5	2-FPh	*i*-Bu	Ph	56	75:25	**5e**
6	2-MePh	*i*-Bu	Ph	40	91:9	**5f**
7	3-furyl	*i*-Bu	Ph	82	84:16	**5g**
8	3-thienyl	*i*-Bu	Ph	69	81:19	**5h**
9	2-NO_2Ph	Et	Ph	73	85:15	**5i**
10	2-MePh	Et	Ph	70	82:18	**5j**
11	*i*-Pr	Et	Ph	39	83:17	**5k**
12	2-NO_2Ph	Me	Ph	62	90:10	**5l**
13	*i*-Pr	Me	Ph	33	92:8	**5m**
14[d]	4-NO_2Ph	Me	Me	48		**5n**

[a]Percent yield is the isolated yield for both diastereomers of **5**. [b]Diastereomeric ratio (dr) determined by GC−MS and ^{1}H NMR analysis of crudes. [c]Entry 1: base = *n*-BuLi, salt additive = $MgCl_2$ (M^+ = MgCl). Entry 2: base = NaHMDS (M^+ = Na). Entries 3−14 (except 13): base = *n*-BuLi (M^+ = Li). Entry 13: base = *n*-BuLi, salt additive = CuI (M^+ = Cu). [d]3 equiv of dimethylketene used.

betaine formation to proceed efficiently. A second possible effect is that, under certain conditions, the additive $MgCl_2$ may enable greater organization (through chelation) in the transition state for [3,3]-sigmatropic rearrangement of **F** to **G** (Scheme 2). However, no significant effect on diastereoselectivity was observed (Table 1, entry 3 vs 6). In most subsequent substrate investigations, the simple system of *n*-BuLi as base proved most general (see Table 2). While in most cases the reaction was allowed to proceed overnight, a simple modification involving heating the reaction to 50 °C, following ketene addition, led to a reduction in total reaction time from ca. 20 to 4 h (see the Experimental Section), with only slight loss of diastereoselectivity (Table 1, entry 8). Interestingly, during this study we found that an unexpected 3,4-disubstituted regioisomer of the γ-lactone, **5a**, was formed as the major product (with no regioisomer **C** detected), and so it appeared that an unanticipated rearrangement of enolate **B** was occurring (Scheme 1). Our revised mechanism is discussed later in this paper (Scheme 2).

We then investigated the substrate scope of the reaction with respect to variation of aldehyde and ketene structure (Table 2). Very good diastereoselectivity (dr up to 92:8) in γ-lactone formation was observed with unsymmetrical ketenes (e.g., entry 3 vs entry 9 vs entry 12, Table 2). Formation of the *trans*-isomer as the major diastereomer was confirmed by X-ray crystallographic analysis of the major diastereomer of **5o**, derived from isobutylphenylketene and 4-NO_2PhCHO (see the

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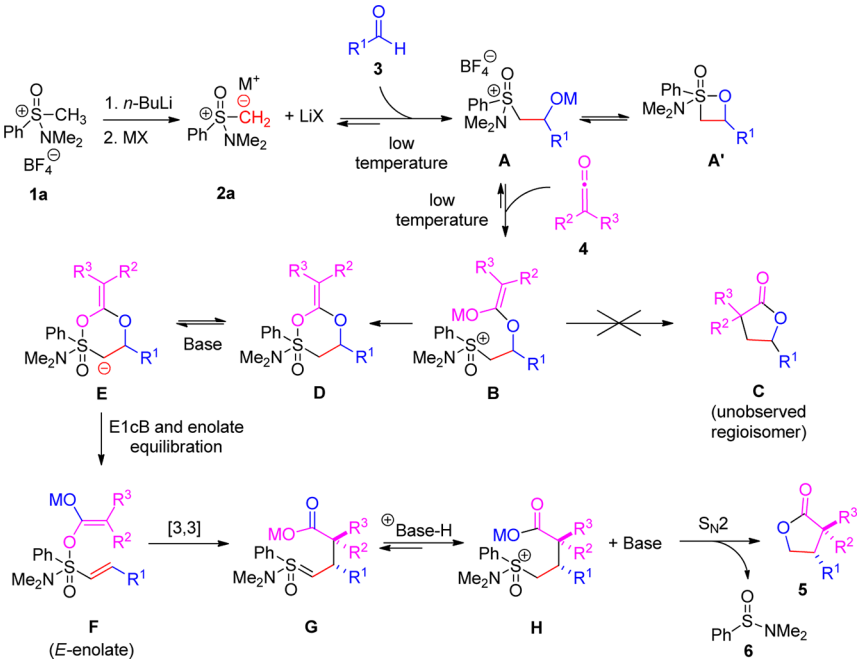
Scheme 2. Possible Reaction Mechanism



Experimental Section). Significantly, the methodology was found to be versatile enough to tolerate ketenes of quite different reactivity; including dimethylketene, alkylarylketenes (entry 1 vs entry 11, entry 13 and entry 14), and even diphenylketene (35−50% yields, not shown in Table 2). Furthermore, the level of diastereoselectivity was found to be good for *ortho*-substituted aromatic aldehydes (entry 3−6), heteroaromatic substituted aldehydes (e.g., entry 7), and the α-branched aliphatic aldehyde, isobutyraldehyde (entry 13). Generally, best yields of γ-lactone were obtained with aromatic aldehydes (≥56% for 9 examples, up to 93%), while with one exception, yields with aliphatic aldehydes were more modest (ca. 30−40%). The lower yields for the aliphatic aldehyde-derived lactones may be attributed to side reactions involving enolates derived from methylphenylketene or ethylphenylketene (e.g., **F** in Scheme 2).

We tentatively propose the mechanism below for the new reaction (Scheme 2). Ylide **2a** adds to aldehyde **3** to give betaine **A**, most likely in equilibrium with oxathietane **A′**.[11] A crossover experiment, with 4-NO_2PhCHO added 1.5 h after PhCHO (followed by isobutylphenylketene), gave a mixture of lactones **5b** (5%) and **5o** (95%), suggesting that betaine/oxathietane formation is reversible under our reaction conditions (see the Experimental Section for details). Reaction of betaine **A** with ketene **4** gives rise to enolate **B**. Enolate **B** is formed stereoselectively as an *E*-enolate (for M = Li) at this point. Direct cyclization of **B** to give γ-lactone regioisomer **C** was not observed. Complete regioselectivity for γ-lactone regioisomer **5** was seen in all cases − no regioisomer **C** was ever detected by GC−MS and ^{1}H NMR analysis of the crude products. Presumably, cyclization of enolate **B** to give six-membered sulfurane oxide **D** is faster than formation of lactone **C**. Many examples of cyclic sulfurane oxides, even optically active ones, are known.[16,17] Deprotonation of **D** by a base (e.g., ylide **2a**) gives sulfurane oxide anion **E**, which then undergoes E1cB elimination to give enolate **F**.[18] We propose that enolate **F** undergoes equilibration to the thermodynamically more stable *E*-enolate geometry under the reaction conditions (final geometry as depicted in Scheme 2). Enolate **F** then undergoes a [3,3]-sigmatropic rearrangement in stereoselective fashion, presumably via a chair transition state, to afford carboxylate **G**. The latter proposed rearrangement is reminiscent of that observed by Marino and co-workers in the reaction of vinyl sulfoxides with dichloroketene.[19] Protonation of **G** gives **H**, which undergoes intramolecular S_N2 (5-*exo-tet*) cyclization to provide *trans*-γ-lactone **5**. Further experiments are being conducted to elaborate details of the reaction mechanism.[20]

In summary, we have developed a new diastereoselective reaction that provides access to γ-lactones. Standout features of the method are that it affords direct access to *trans*-γ-lactones via an unprecedented extension to the Johnson−Corey−Chaykovsky reaction, in good yields (up to 95%), and with good diastereoselectivity (11 examples with dr ≥82:18, up to 92:8). Current studies are focused on developing an asymmetric variant of the new reaction, carrying out detailed mechanistic investigations, and exploring the generality of the described strategy for the synthesis of other 5-membered ring systems.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere techniques unless otherwise stated. THF was dried using a sodium/benzophenone ketyl still, and *N*,*N*-dimethylethylamine was distilled from potassium hydroxide under nitrogen.[21] 2-Phenylacetic acid, 2-phenylpropanoic acid, 2-phenylbutanoic acid, 1-bromo-2-methylpropane, diphenylacetyl chloride, 2-bromo-2-methylpropionyl bromide, thionyl chloride, 2-nitrobenzaldehyde, 4-nitrobenzaldehyde, 2-chlorobenzaldehyde, α-D-benzaldehyde, methylphenyl sulfoxide, sodium azide, formaldehyde, formic acid, trimethyloxonium tetrafluoroborate, and *n*-butyllithium (2.5 M in hexane) were used as received. Isobutyraldehyde, *o*-tolualdehyde, 2-fluorobenzaldehyde, and benzaldehyde were distilled prior to use.

Iatrobeads (neutral silica, 60 μM particle size) and TLC plates (UV254, 250 μM) were used as received. (Dimethylamino)-methylphenyl oxosulfonium fluoroborate was synthesized according to a literature procedure.[22,23] Diphenylketene, methylphenylketene,

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ethylphenylketene, and isobutylphenylketene were prepared through amine-mediated dehydrohalogenation.[24a−c] Dimethylketene was prepared through zinc-mediated dehalogenation of 2-bromo-2-methylpropionyl bromide.[24d]

NMR spectra were recorded on a 200 MHz spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C) and on a 400 MHz 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. 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). High resolution mass spectra were recorded on an Accurate-Mass Q-TOF LC/MS with ESI as ionization method. IR spectra were recorded on an IR spectrometer.

Diastereoselectivity for γ-lactone formation was determined by GC−MS analysis of the crude product and corroborated by ^{1}H NMR analysis in each case.

General Procedure A for Preparation of γ-Lactones. (Dimethylamino)methylphenyl oxosulfonium fluoroborate **1a** was placed under high vacuum for 0.5 h. After drying, the sulfoxonium salt **1a** (68 mg, 0.25 mmol) was suspended in anhydrous THF (1.5 mL) and stirred at −78 °C. *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol) or NaHMDS (1 M in THF, 0.25 mL, 0.25 mmol, for **5b** only) was added dropwise at −78 °C, and the solution was stirred for 45 min. Aldehyde (0.25 mmol) or aldehyde solution (0.25 mmol solid aldehyde dissolved in 0.5 mL THF) was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, the ketene solution (0.25 mmol ketene in 0.5 mL THF) was added to the reaction over 1 h (15 min for dialkylketene). After being stirred for a further 4 h at −78 °C, the reaction was gradually allowed to warm to room temperature overnight in the cooling bath. The total reaction time was typically 20 h. The solvent was then removed to give the crude product, and the crude product was purified by passing through a plug of neutral silica (50−100 times × crude weight), eluting with an EtOAc/hexane solvent system.

General Procedure B for Preparation of γ-Lactones. (Dimethylamino)methylphenyl oxosulfonium fluoroborate **1a** was placed under high vacuum for 0.5 h. After drying, the sulfoxonium salt **1a** (68 mg, 0.25 mmol) was suspended in anhydrous THF (1.5 mL) and stirred at −78 °C. *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol) was added dropwise at −78 °C, and the reaction was stirred for 45 min. An appropriate metal salt (0.25−0.50 mmol) was then added to the reaction solution under a positive pressure of nitrogen. Transmetalation was assumed to be complete after 15 min. Aldehyde (0.25 mmol) or aldehyde solution (0.25 mmol solid aldehyde dissolved in 0.5 mL THF) was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, the ketene solution (0.25 mmol ketene in 0.5 mL THF) was added to the reaction over 1 h. After being stirred for a further 4 h at −78 °C, the reaction was gradually allowed to warm to room temperature overnight in the cooling bath. The total reaction time was typically 20 h. The solvent was then removed to give the crude product and the crude product was purified by passing through a plug of neutral silica (50−100 times × crude weight), eluting with an EtOAc/hexane solvent system.

*3-Isobutyl-4-isopropyl-3-phenyldihydrofuran-2(3H)-one (**5a**).* The reaction was performed following general procedure B with $MgCl_2$ (0.5 mmol, 2 equiv) using sulfoxonium salt **1a**, isobutyraldehyde, and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). **5a** was isolated as a colorless oil (60 mg, 93% yield) in 95% purity and with a dr = 88:12 as determined by GC−MS analysis of the crude product: IR (thin film) 1764 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.38−7.32 (m, 4H), 7.29−7.24 (m, 1H), 4.21 (dd, *J* = 6.6 Hz, 9.3 Hz, 1H), 4.11 (dd, *J* = 5.8 Hz, 9.3 Hz, 1H), 2.64 (app q, *J* = 6.2 Hz, 1H), 2.07−1.99 (m, 1H), 1.97−1.86 (m, 2H), 1.72−1.63 (m, 1H), 0.89−0.87 (m, 6H), 0.81−0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 180.1, 140.2, 128.5, 127.4, 127.3, 67.3, 53.7, 53.3, 38.5, 26.4, 24.4, 24.2, 24.2, 21.8, 18.9; MS (EI 70 eV) 260, 204, 161, 117, 91 *m*/*z*; (M$^+$ + H) HRMS *m*/*z* calcd for $C_{17}H_{25}O_2^+$ 261.1855, found 261.1861.

*3-Isobutyl-3,4-diphenyldihydrofuran-2(3H)-one (**5b**).* The reaction was performed following General Procedure A, with NaHMDS as base instead of *n*-BuLi, and using sulfoxonium salt **1a**, benzaldehyde, and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). The crude product was purified through a plug of neutral silica eluting with 1.5% EtOAc/hexane, and **5b** was isolated as a colorless oil (44 mg, 60% yield) with a dr = 83:17 as determined by GC−MS analysis of the crude product: IR (thin film) 1769, 1002 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.19−7.09 (m, 6H), 6.83−6.81 (m, 2H), 6.71−6.68 (m, 2H), 4.56 (dd, *J* = 7.4 Hz, 9.1 Hz, 1H), 4.32 (t, *J* = 9.3 Hz, 1H), 3.86 (dd, *J* = 7.4 Hz, 9.6 Hz, 1H), 2.06−1.97 (m, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer 178.9, 136.7, 135.6, 128.9, 128.1, 128.0, 127.8, 127.6, 127.1, 68.7, 57.0, 51.6, 44.4, 25.2, 24.2, 23.9; MS (EI 70 eV) 294, 238, 193, 131, 103, 77 *m*/*z*; (M$^+$ + H) HRMS *m*/*z* calcd for $C_{20}H_{23}O_2^+$ 295.1698, found 295.1693.

*3-Isobutyl-4-(2-nitrophenyl)-3-phenyldihydrofuran-2(3H)-one (**5c**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-nitrobenzaldehyde, and isobutylphenylketene. The crude product was purified through a plug of neutral silica eluting with 3% EtOAc/hexane, and **5c** was isolated as a white solid (60 mg, 70% yield) with a dr = 87:13 as determined by GC−MS analysis of the crude product: IR (thin film) 1768, 1524, 1349 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.60−7.58 (m, 1H), 7.30−7.26 (m, 1H), 7.20−7.15 (m, 3H), 7.10−7.00 (m, 4H), 4.87 (dd, *J* = 7.0 Hz, 9.9 Hz, 1H), 4.63 (dd, *J* = 2.6 Hz, 7.0 Hz, 1H), 4.44 (dd, *J* = 2.6 Hz, 9.9 Hz, 1H), 2.25−2.13 (m, 2H), 1.85−1.78 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.66 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 177.6, 149.8, 137.0, 134.5, 132.8, 129.2, 128.2, 128.1, 128.1, 127.0, 124.5, 70.7, 56.3, 47.7, 47.6, 25.0, 24.6, 24.1; MS (EI 70 eV) 339, 283, 266, 237, 103, 81, 77 *m*/*z*; (M$^+$ + H) HRMS *m*/*z* calcd for $C_{20}H_{22}NO_4^+$ 340.1549, found 340.1548.

*4-(2-Chlorophenyl)-3-isobutyl-3-phenyldihydrofuran-2(3H)-one (**5d**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-chlorobenzaldehyde, and isobutylphenylketene. The crude product was purified through a plug of neutral silica eluting with 1.5% EtOAc/hexane, and **5d** was isolated as a colorless oil (35 mg, 43% yield) with a dr = 83:17 as determined by GC−MS analysis of the crude product: IR (thin film) 1769 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.19−7.15 (m, 3H), 7.12−7.06 (m, 3H), 7.01−6.96 (m, 1H), 6.93−6.89 (m, 1H), 6.65−6.63 (m, 1H), 4.72 (dd, *J* = 7.2 Hz, 9.4 Hz, 1H), 4.46 (dd, *J* = 4.8 Hz, 7.2 Hz, 1H), 4.31(dd, *J* = 4.7 Hz, 9.4 Hz, 1H), 2.21−2.17 (m, 2H), 1.99−1.92 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 178.3, 137.1, 136.6, 134.2, 129.6, 129.2, 128.5, 128.4, 127.9, 127.0, 126.9, 70.5, 56.6, 49.1, 47.1, 25.0, 24.9, 24.2; MS (EI 70 eV) 328, 272, 227, 131, 103, 91, 77 *m*/*z*; (M$^+$ + H) HRMS *m*/*z* calcd for $C_{20}H_{22}ClO_2^+$ 329.1308, found 329.1304.

*4-(2-Fluorophenyl)-3-isobutyl-3-phenyldihydrofuran-2(3H)-one (**5e**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-fluorobenzaldehyde, and isobutylphenylketene. The crude product was purified through a plug of neutral silica eluting with 2% EtOAc/hexane, and **5e** was isolated as a colorless oil (44 mg, 56% yield) with a dr =75:25 as determined by GC−MS analysis of the crude product: IR (thin film) 1769 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 7.14−7.02 (m, 6H), 6.90−6.85 (m, 1H), 6.82−6.78 (m, 1H), 6.54−6.50 (m, 1H), 4.63 (dd, *J* = 7.4 Hz, 9.2 Hz, 1H), 4.35 (dd, *J* = 7.0 Hz, 9.2 Hz, 1H), 4.21 (t, *J* = 7.2 Hz, 1H), 2.17−2.08 (m, 2H), 2.03−1.94 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer: δ 178.4, 160.8 (d, *J* = 244.0 Hz), 137.2, 129.6 (d, *J* = 8.5 Hz), 129.2 (d, *J* = 8.6 Hz), 128.1, 128.0, 127.2, 124.7 (d, *J* = 13.7 Hz), 124.0 (d, *J* = 3.4 Hz), 115.4 (d, *J* = 23.1 Hz), 69.1, 56.6, 45.9, 45.2, 25.1, 25.0, 24.0; MS (EI 70 eV) 312, 269, 256, 211, 131, 103, 91, 77 *m*/*z*; (M$^+$ + H) HRMS *m*/*z* calcd for $C_{20}H_{22}FO_2^+$ 313.1604, found 313.1605.

*3-Isobutyl-3-phenyl-4-o-tolyldihydrofuran-2(3H)-one (**5f**).* The reaction was performed following general procedure A using

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sulfoxonium salt **1a**, 2-methylbenzaldehyde, and isobutylphenylketene. The crude product was purified through a plug of neutral silica eluting with 2% EtOAc/hexane, and **5f** was isolated as a colorless oil (31 mg, 40% yield) with a dr = 91:9 as determined by GC−MS analysis of the crude product: IR (thin film) 1766 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.10−7.03 (m, 5H), 7.00−6.95 (m, 2H), 6.89−6.84 (m, 1H), 6.50 (d, J = 7.8 Hz, 1H), 4.67 (dd, J = 7.1 Hz, 9.3 Hz, 1H), 4.32 (dd, J = 5.6 Hz, 9.3 Hz, 1H), 4.02 (dd, J = 5.6 Hz, 7.0 Hz, 1H), 2.28 (s, 3H), 2.22−2.07 (m, 2H), 2.00−1.90 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer: δ 178.8, 136.9, 136.5, 136.1, 130.5, 128.6, 128.1, 127.7, 127.2, 127.0, 126.0, 70.9, 56.9, 49.2, 46.9, 25.0, 24.9, 24.4, 20.6; MS (EI 70 eV): 308, 252, 118, 103 m/z; (M^+ + H) HRMS m/z calcd for $C_{21}H_{25}O_2^+$ 309.1855, found 309.1850.

*4-(Furan-3-yl)-3-isobutyl-3-phenyldihydrofuran-2(3H)-one (**5g**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 3-furalcarboxaldehyde, and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). The crude product was purified through a plug of neutral silica eluting with 5% EtOAc/hexane, and **5g** was isolated as a yellow oil which was crystallized from MeOH to give a pale yellow solid (58 mg, 82% yield) with a dr = 84:16 as determined by GC−MS analysis of the crude product: IR (thin film) 1775 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 7.22−7.18 (m, 5H), 6.99−6.96 (m, 3H), 4.48 (dd, J = 7.4 Hz, 8.8 Hz, 1H), 4.06 (dd, J = 8.9 Hz, 10.2 Hz, 1H), 3.81 (dd, J = 7.4 Hz, 10.2 Hz, 1H), 2.04 (d, J = 1.0 Hz, 2H), 1.96−1.87 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 179.0, 142.9, 140.5, 136.8, 128.1, 127.8, 120.3, 119.5, 110.2, 68.6, 56.4, 43.7, 42.3, 25.3, 25.3, 24.1; MS (EI 70 eV) 284, 241, 228, 174, 131, 103, 91; (M^+ + H) HRMS m/z calcd for $C_{18}H_{21}O_3^+$ 285.1491, found 285.1487.

*3-Isobutyl-3-phenyl-4-(thiophene-3-yl)dihydrofuran-2(3H)-one (**5h**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 3-thiophenecarboxaldehyde, and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). The crude product was purified through a plug of neutral silica eluting with 5% EtOAc/hexane, and **5h** was isolated as a yellow oil (52 mg, 69% yield) with a dr = 81:19 as determined by GC−MS analysis of the crude product: IR (thin film) 1772 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.40−7.38 (m, 1H), 7.18−7.11 (m, 3H), 6.85−6.82 (m, 2H), 6.61−6.60 (m, 1H), 6.42 (dd, J = 1.2 Hz, 5.0 Hz, 1H), 4.52 (dd, J = 7.3 Hz, 8.9 Hz, 1H), 4.21 (dd, J = 7.3 Hz, 10.1 Hz, 1H), 4.01 (dd, J = 7.3 Hz, 10.1 Hz, 1H), 2.05 (d, J = 5.4 Hz, 2H), 2.03−1.94 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 178.9, 136.8, 135.9, 127.9, 127.7, 127.4, 127.3, 125.5, 123.0, 68.7, 56.9, 46.8, 43.9, 25.3, 25.2, 23.9; MS (EI 70 eV): 284, 241, 228, 174, 131, 103, 91; (M^+ + H) HRMS m/z calcd for $C_{18}H_{21}SO_2^+$ 301.1262, found 301.1261.

*3-Ethyl-4-(2-nitrophenyl)-3-phenyldihydrofuran-2-one (**5i**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-nitrobenzaldehyde, and ethylphenylketene. The crude product was purified through a plug of neutral silica eluting with 2% EtOAc/hexane, and **5i** was isolated as a white solid (57 mg, 73% yield) with a dr = 85:15 as determined by GC−MS analysis of the crude product: IR (thin film) 1770, 1526, 1352 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.64−7.61 (m, 1H), 7.27−7.21 (m, 2H), 7.11−7.08 (m, 3H), 7.05−7.03 (m, 2H), 6.83−6.80 (m, 1H), 4.77 (dd, J = 7.2 Hz, 9.6 Hz, 1H), 4.65 (dd, J = 4.7 Hz, 7.2 Hz, 1H), 4.44−4.41 (m, 1H), 2.30−2.21 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 177.7, 150.3, 136.3, 133.2, 132.5, 129.6, 128.4, 128.2, 128.1, 127.3, 124.5, 70.3, 57.5, 46.1, 31.2, 9.1; MS (EI 70 eV): 311, 117, 91 m/z; (M^+ + H) HRMS m/z calcd for $C_{18}H_{18}NO_4^+$ 312.1236, found 312.1234.

*3-Ethyl-3-phenyl-4-o-tolyldihydrofuran-2-one (**5j**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-methylbenzaldehyde, and ethylphenylketene. The crude product was purified through a plug of neutral silica eluting with 2% EtOAc/hexane, and **5j** was isolated as a white solid (54 mg, 70% yield) with a dr = 82:18 as determined by GC−MS analysis of the crude product: IR (thin film) 1769 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.17−6.17 (m, 9H), 4.53 (dd, J = 7.4 Hz, 9.0 Hz, 1H), 4.31 (t, J = 8.8 Hz, 1H), 4.14 (t, J = 7.7 Hz, 1H), 2.36 (s, 3H), 2.23−2.12 (m, 2H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 179.0, 136.7, 136.5, 134.4, 130.7, 128.7, 128.4, 128.1, 127.4, 127.4, 125.7, 70.1, 57.9, 47.0, 29.7, 20.6, 9.2; MS (EI 70 eV): 280, 146, 118 m/z; (M^+ + H) HRMS m/z calcd for $C_{19}H_{21}O_2^+$ 281.1543, found 281.1542.

*3-Ethyl-4-isopropyl-3-phenyldihydrofuran-2-one (**5k**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, isobutyraldehyde, and ethylphenylketene. The crude product was purified through a plug of neutral silica eluting with 5% EtOAc/hexane, and **5k** was isolated as a colorless oil (23 mg, 39% yield) with a dr = 83:17 as determined by GC−MS analysis of the crude product: IR (thin film) 1766 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.38−7.24 (m, 5H), 4.23 (dd, J = 7.0 Hz, 9.3 Hz, 1H), 4.07 (dd, J = 6.7 Hz, 9.3 Hz, 1H), 2.55 (app q, J = 6.8 Hz, 1H), 2.17−2.09 (m, 1H), 2.06−1.95 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 180.2, 140.7, 128.7, 127.8, 127.3, 68.1, 54.3, 49.8, 29.6, 26.7, 23.2, 22.0, 19.6; MS (EI 70 eV) 232, 145, 117, 91 m/z; (M^+ + H) HRMS m/z calcd for $C_{15}H_{21}O_2^+$ 233.1542, found 233.1543.

*3-Methyl-4-(2-nitrophenyl)-3-phenyldihydrofuran-2(3H)-one (**5l**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, 2-nitrobenzaldehyde, and methylphenylketene. The crude product was purified through a plug of neutral silica eluting with 5% EtOAc/hexane, and **5l** was isolated as a white solid (46 mg, 62% yield) with a dr = 90:10 as determined by GC−MS analysis of the crude product: IR (thin film) 1771, 1524, 1351 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.69−7.66 (m, 1H), 7.30−7.21 (m, 2H), 7.16−7.12 (m, 3H), 6.96−6.93 (m, 2H), 6.65−6.63 (m, 1H), 4.69 (dd, J = 7.2 Hz, 9.3 Hz, 1H), 4.58 (t, J = 7.0 Hz, 1H), 4.45 (dd, J = 6.7 Hz, 9.2 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 179.3, 150.7, 137.2, 132.3, 131.3, 129.5, 128.52, 128.50, 127.7, 127.6, 124.7, 69.5, 53.6, 47.5, 24.5; MS (EI 70 eV): 297, 132, 104, 77 m/z; (M^+ + H) HRMS m/z calcd for $C_{17}H_{16}NO_4^+$ 298.1079, found 298.1078.

*4-Isopropyl-3-methyl-3-phenyldihydrofuran-2(3H)-one (**5m**).* The reaction was performed following general procedure B with CuI (0.5 mmol, 2 equiv) using sulfoxonium salt **1a**, isobutyraldehyde, and methylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with saturated sodium thiosulfate solution (2 × 10 mL) and H_2O (2 × 10 mL). The crude product was purified through a plug of neutral silica eluting with 2% EtOAc/hexane, and **5m** was isolated as a colorless oil (18 mg, 33% yield) with a dr = 92:8 as determined by GC−MS analysis of the crude product: IR (thin film) 1771 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.38−7.24 (m, 5H), 4.41 (dd, J = 7.5 Hz, 9.2 Hz, 1H), 4.03 (t, J = 9.1 Hz, 1H), 2.59−2.53 (m, 1H), 1.95−1.83 (m, 1H), 1.58 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 181.3, 142.7, 128.6, 127.2, 126.8, 69.0, 54.7, 50.3, 27.5, 21.3, 20.0, 15.9; MS (EI 70 eV) 218, 131, 118, 91 m/z; (M^+ + H) HRMS m/z calcd for $C_{14}H_{19}O_2^+$ 219.1385; found: 219.1388.

*3,3-Dimethyl-4-(4-nitrophenyl)dihydrofuran-2-one (**5n**).* The reaction was performed following general procedure A using (dimethylamino)methylphenyl oxosulfonium fluoroborate **1a**, 4-nitrobenzaldehyde, and dimethylketene (0.75 mmol, 3 equiv), with the ketene solution being added over 15 min. The crude product was purified through a plug of neutral silica eluting with 10% EtOAc/hexane, and **5n** was isolated as a white solid (23 mg, 48% yield): IR (thin film) 1769, 1519, 1349 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) δ 8.26−8.22 (m, 2H), 7.39−7.36 (m, 2H), 4.64 (dd, J = 7.2 Hz, 9.5 Hz, 1H), 4.53 (dd, J = 7.6 Hz, 9.5 Hz, 1H), 3.55 (t, J = 7.4 Hz, 1H), 1.40 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 147.8, 144.4, 129.1, 124.2, 68.6, 52.4, 43.6, 24.7, 20.1; MS (EI 70 eV) 235, 174, 130, 115, 91 m/z; (M^+ + H) HRMS m/z calcd for $C_{12}H_{14}NO_4^+$ 236.0923, found 236.0919.

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*3-Isobutyl-4-(4-nitrophenyl)-3-phenyldihydrofuran-2-one (**5o**).* The reaction was performed following general procedure A using sulfoxonium salt **1a**, *n*-BuLi as base, 4-nitrobenzaldehyde, and isobutylphenylketene. The crude product was purified through a plug of neutral silica eluting with 20% EtOAc/hexane, and **5o** was isolated as a white solid (37 mg, 44% yield) with a dr = 60:40 as determined by GC−MS analysis of the crude product: IR (thin film) 1771, 1521, 1348 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 8.24−8.21 (m, 2H), 7.44−7.31 (m, 7H), 4.52−4.45 (m, 2H), 4.05 (t, J = 5.4 Hz, 1H), 1.65−1.57 (m, 2H), 1.39−1.33 (m, 1H), 0.63 (d, J = 6.3 Hz, 3H), 0.47 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 178.1, 147.8, 144.9, 138.2, 129.6, 129.2, 128.3, 127.3, 124.2, 69.5, 56.0, 53.8, 41.3, 24.5, 24.4, 24.4; MS (EI 70 eV) 339, 296, 283, 192, 131, 103, 77 m/z; (M^+ + H); HRMS m/z calcd for $C_{20}H_{22}NO_4^+$ 340.1549, found 340.1545. A sample of the major diastereomer of **5o** was crystallized from hexane and acetone to provide crystals suitable for X-ray crystallographic analysis. See the Supporting Information (CIF) for full details of the crystal structure analysis. The crystal structure shows the *trans*-relative stereochemistry of the major diastereomer of γ-lactone **5o**. The relative stereochemistry of γ-lactones **5a**−**n** was assigned to be *trans* by analogy.

Thermal Procedure: 3-Isobutyl-4-isopropyl-3-phenyldihydrofuran-2(3*H*)-one (5a). The reaction was performed following general procedure B with $MgCl_2$ (0.25 mmol) using sulfoxonium salt **1a**, isobutyraldehyde, and isobutylphenylketene. Fifteen minutes after ketene addition had finished, the reaction was placed in a 50 °C oil bath for 15 min (total reaction time = 4 h). The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). The crude product was purified through a plug of neutral silica eluting with 2.5% EtOAc/hexane. Compound **5a** was isolated as a colorless oil (61.8 mg, 95%) with a dr = 85:15 as determined by GC−MS analysis of the crude product: IR (thin film) 1764 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer δ 7.38−7.32 (m, 4H), 7.29−7.24 (m, 1H), 4.21 (dd, J = 6.6 Hz, 9.3 Hz, 1H), 4.11 (dd, J = 5.8 Hz, 9.3 Hz, 1H), 2.64 (app q, J = 6.2 Hz, 1H), 2.07−1.99 (m, 1H), 1.97−1.86 (m, 2H), 1.72−1.63 (m, 1H), 0.89−0.87 (m, 6H), 0.81−0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer δ 180.1, 140.2, 128.5, 127.4, 127.3, 67.3, 53.7, 53.3, 38.5, 26.4, 24.4, 24.2, 24.2, 21.8, 18.9; MS (EI 70 eV) 260, 204, 161, 117, 91 m/z; (M^+ + H) HRMS m/z calcd for $C_{17}H_{25}O_2^+$ 261.1855, found 261.1861.

Crossover Experiment of PhCHO and 4-NO_2PhCHO. The reaction was performed following general procedure A with some modifications using sulfoxonium salt **1a**, *n*-BuLi as base, benzaldehyde, 4-nitrobenzaldehyde, and isobutylphenylketene. After addition of *n*-butyllithium to sulfoxonium salt **1a** and 45 min of stirring at −78 °C, benzaldehyde dissolved in THF was added dropwise, and the reaction was stirred for 1.5 h at −78 °C. Then 4-nitrobenzaldehyde, dissolved in THF, was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, a THF solution of isobutylphenylketene was added as per General Procedure A. The reaction was worked up by diluting the crude product solution with ether (10 mL), and washing the organics with H_2O (2 × 10 mL). The crude product was analyzed by GC−MS, and it was determined that the reaction proceeded with a conversion of >95%, being composed of ca. 5% **5b** (dr = 86:14) and ca. 95% **5o** (dr = 62:38): MS (EI 70 eV) for **5b**: 294, 238, 193, 131, 103, 77 m/z; MS (EI 70 eV) for **5o** 339, 296, 283, 192, 131, 103, 77 m/z.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR spectra, ^{13}C NMR spectra, and GC traces for all products and X-ray data for **5o** (CIF). This information 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) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285−292.

(2) (a) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1985**, *24*, 94−110. (b) Koch, S. S. C.; Chamberlain, A. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: New York, 1995; Vol. *16*, pp 687−725.

(3) (a) de March, P.; Figueredo, M.; Font, J.; Raya, J. *Org. Lett.* **2000**, *2*, 163−165. (b) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823−9826.

(4) (a) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483. (b) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, 1402−1403. (c) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (d) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208.

(5) (a) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509−5512. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2283−2316. (c) Harcken, C.; Brückner. *Angew. Chem., Int. Ed.* **1997**, *36*, 2750−2752. (d) Park, H. S.; Kwon, D. W.; Lee, K.; Kim, Y. H. *Tetrahedron Lett.* **2008**, *49*, 1616−1618. (e) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298−3300. (f) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329−7332.

(6) Murahashi, S.; Ono, S.; Imada, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366−2368.

(7) Chiang, P.-C.; Bode, J. W. N-Heterocyclic Carbene Catalyzed Reactions of α-Functionalized Aldehydes. In *Science of Synthesis Reference Library, Asymmetric Organocatalysis, Vol. 1, Lewis Base and Acid Catalysts*; List, B., Ed.; Thieme: Stuttgart, 2012; Chapter 1.1.15, pp 639−672.

(8) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500−3501.

(9) (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (b) Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 417−423. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem, Soc.* **1965**, *87*, 1353−1364. (d) Johnson, C. R.; Janiga, E. R.; Haake, M. *J. Am. Chem. Soc.* **1968**, *90*, 3890−3891. (e) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341−347.

(10) (a) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747−5756. (b) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1984**, *106*, 6117−6119.

(11) (a) Okuma, K.; Tanaka, Y.; Ohta, H. *J. Am. Chem. Soc.* **1981**, *103*, 5976−5977. (b) Ohno, F.; Kawashima, T.; Okazaki, R. *J. Am. Chem. Soc.* **1996**, *118*, 697−698. (c) Kawashima, T.; Ohno, F.; Okazaki, R.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **1996**, *118*, 12455−12456.

(12) Wu, J.-Y.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *J. Org. Chem.* **2008**, *73*, 9137−9139.

(13) (a) Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. *J. Am. Chem. Soc.* **2012**, *134*, 2942−2945. (b) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784−1787.

(14) (a) Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1988**, *53*, 5974−5977. (b) Oda, R.; Muneimiya, S.; Okano, M. *J. Org. Chem.* **1961**, *26*, 1341−1343.

(15) Phosphonium, sulfonium, and trimethylsulfoxonium ylides were found to be inferior to **2a** in facilitating formation of **5a**.

(16) (a) Martin, J. C.; Perozzi, E. F. *J. Am. Chem. Soc.* **1974**, *96*, 3155−3168. (b) Rongione, J. C.; Martin, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 1637−1638.
(17) Drabowicz, J.; Martin, J. C. *Pure Appl. Chem.* **1996**, *68*, 951−956.
(18) Lau, P. H. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 5490−5491.
(19) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687−7689.
(20) (a) When PhCDO was used as a substrate in reaction with **2a** and isobutylphenylketene, D-**5b** was obtained with >95% conversion and with deuterium incorporated at C4. (b) When ^{18}O-labeled benzaldehyde was used as a substrate, ^{18}O was found to be fully incorporated into the lactone **5b**, rather than into sulfinamide byproduct **6**.
(21) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th Ed.; Butterworth Heinemann: Boston, 2002.
(22) (a) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594−6598. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418−7423.
(23) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *6*, 909−912.
(24) (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007. (b) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. *J. Am. Chem. Soc.* **1985**, *107*, 5391−5396. (c) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578−1579. (d) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358−6360.

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