EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Diastereoselective Synthesis of γ-Lactones through Reaction of Sulfoxonium Ylides, Aldehydes and Ketenes: Substrate Scope and Mechanistic Studies

Authors: Nicholas Peraino, Mukulesh Mondal, Han-Jen Ho, Antoine Beuque, Evan Viola, Melanie Gary, Kraig Wheeler, and Nessan Joseph Kerrigan

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001233

Link to VoR: https://doi.org/10.1002/ejoc.202001233

WILEY-VCH

Diastereoselective Synthesis of γ-Lactones through Reaction of Sulfoxonium Ylides, Aldehydes and Ketenes: Substrate Scope and Mechanistic Studies

Nicholas J. Peraino,[a] Mukulesh Mondal,[a] Han-Jen Ho,[a] Antoine Beuque,[b] Evan Viola,[b] Melanie Gary,[a] Kraig A. Wheeler[c] and Nessan J. Kerrigan[b],*

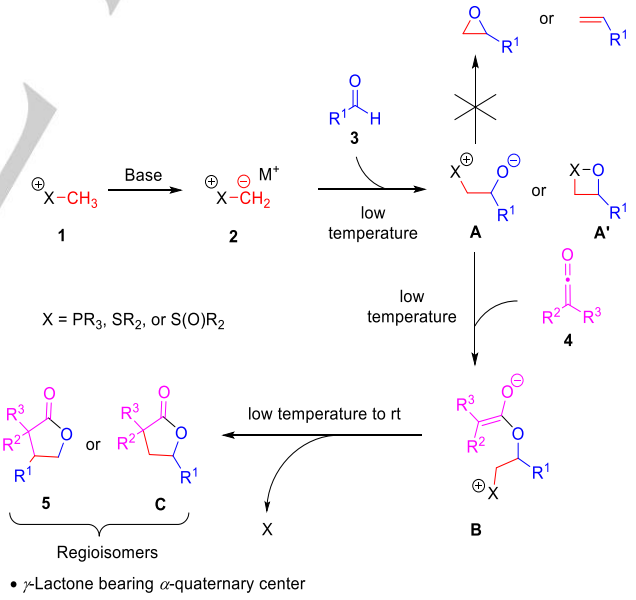
Abstract: In this article we describe the synthesis of γ-lactones through the reaction of sulfoxonium ylides, aldehydes, and disubstituted ketenes. The one-pot sequential method provides access to γ-lactones from disubstituted ketenes, in moderate to excellent yields, and with good diastereoselectivity favoring the *trans*-diastereomer (dr up to 92:8). The reaction mechanism was investigated by performing labeling, crossover and various control experiments. The results of those experiments support the reaction mechanism involving betaine formation, reaction of the betaine with a ketene to form an enolate intermediate, [3,3]-sigmatropic rearrangement of an enolate intermediate, and finally 5-*exo*-*tet* cyclization to afford the γ-lactone product.

Introduction

γ-Lactones are a class of molecule that is found in 10% of all natural products.[1] γ-Lactones demonstrate an impressive range of biological activity. Bicyclic fused γ-lactones, such as parthenolide and costunolide, and certain monocyclic γ-lactones bearing an α-methylene group have demonstrated selectivity against pancreatic cancer cell lines.[2] They have also exhibited strong antifungal, antibiotic, antiviral, and anti-inflammatory activity, and as a result have attracted much interest as lead compounds for the development of pharmaceuticals.[1,2] γ-Lactones have also been shown to act as versatile intermediates in complex molecule synthesis.[3]

While there are a number of highly efficient methods for the stereoselective synthesis of γ-lactones, many methods suffer from disadvantages such as limited substrate scope, multistep approaches to starting materials for intramolecular reactions, or the use of expensive reagents/catalysts (e.g. SmI_2).[4] Methods faciltating direct generation of γ-lactones bearing an α-quaternary center or aryl substituent at the α-position are particularly rare.[5,6]

As part of our research on the development of new reactions of ketenes[7], we previously reported that the reaction of onium ylides, aldehydes and disubstituted ketenes provides access to γ-lactones bearing an α-quaternary center.[8] Our original strategy was as follows: reaction of ylide **2** (generated from salt **1**) and aldehyde **3** under mild conditions (at −78 °C) would provide access to betaine **A** or an oxacycle **A'** (e.g. oxaphosphetane). Cyclization to give epoxide (Johnson-Corey-Chaykovsky reaction) or retro [2 + 2]-cycloaddition to give alkene (Wittig reaction) would be slowed at low temperature (Scheme 1).[9] We suspected that betaine intermediate **A** or oxacycle **A'** could be intercepted by a ketene **4** to generate an enolate **B** at low temperature. On warming, the enolate intermediate **B** would then be expected to undergo 5-*exo*-*tet* cyclization to generate the 3,5-substituted γ-lactone product **C**, or undergo rearrangement and cyclization to give the 3,4-substituted γ-lactone regioisomer **5**, along with loss of the leaving group X (Scheme 1). In this paper we describe our optimization studies, a full study of the methodology's substrate scope, and various labelling, crossover and control experiments that shed light on the mechanism of the reaction.



Scheme 1. Planned reaction.

Results and Discussion

Reaction optimization. Our studies began with the optimization of the reaction of onium ylides **2a-2h,** generated in situ through reaction of *n*-BuLi with **1a-1h** (Figure 1), PhCHO (or 4-$NO_2C_6H_4CHO$) **3**, and diphenylketene (or methylphenylketene) **4** (Table 1). The aldehyde **3** was added slowly to the ylide **2** at

[a] Dr. N. J. Peraino, Dr. M. Mondal, H.-J. Ho, M. Gary, Department of Chemistry
Oakland University
2200 N. Squirrel Rd, MI 48309, USA
[b] A. Beuque, E. Viola, Dr. N. J. Kerrigan, School of Chemical Sciences
Dublin City University
Glasnevin, Dublin 9, Ireland
nessan.kerrigan@dcu.ie
https://www.dcu.ie/chemistry/people/Nessan-Kerrigan.shtml
[c] Dr. Kraig A. Wheeler, Chemistry Department, Whitworth University, USA

Supporting information for this article is given via a link at the end of the document.

–78 °C, and after that, the ketene was added slowly over 15-60 min at –78 °C to the reaction solution. In each case the reaction was allowed to warm to room temperature overnight.

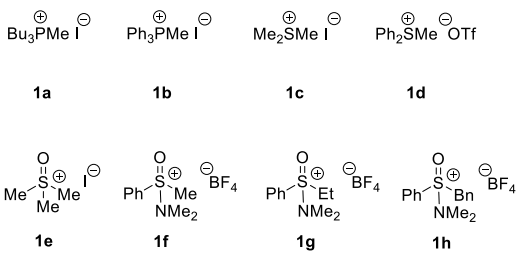


Figure 1. Selected onium salts for ylide generation.

Phosphonium (**2a** and **2b**) and triethylmethylammonium ylides were initially investigated but only *ca*. 6% of lactone **5** was obtained (Table 1, entry 2). We reasoned that the leaving group ability of the phosphine and amine was too poor to allow for efficient cyclization of **B** to proceed.[10] With this in mind we then proceeded to investigate onium salts with better leaving groups (sulfide, sulfoxide, and sulfinamide), such as sulfonium ylides (**2c** and **2d**) and sulfoxonium ylides (**2e** and **2f**). Ultimately, chiral aminosulfoxonium ylide **2f** was determined to be the optimal onium ylide (71-92% conv to γ-lactone), although **2e** also performed well. Carrying out ketene addition at a higher temperature (e.g. –30 °C) led to poor conversion to γ-lactone (<20%).

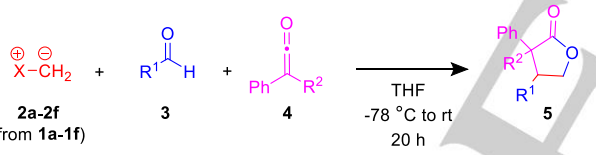
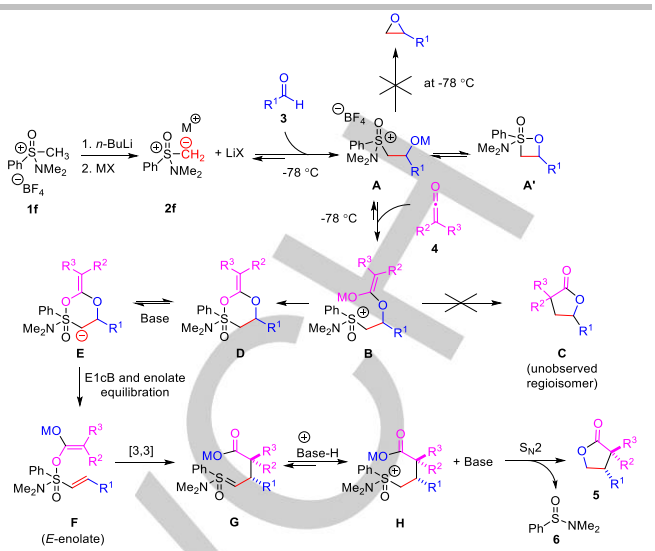


Table 1. Optimization of the Synthesis of γ-Lactones.

Entry	X	R^1	R^2	Conv[a]
1	PBu_3 (**2a**)	Ph	Ph	0
2	PPh_3 (**2b**)	Ph	Ph	6
3	SMe_2 (**2c**)	Ph	Ph	0
4	SPh_2 (**2d**)	Ph	Ph	15
5	$S(O)Me_2$ (**2e**)	Ph	Ph	60
6	$S(O)Me_2$ (**2e**)	Ph	Me	55
7	$S(O)(NMe_2)Ph$ (**2f**)	Ph	Me	90
8	$S(O)(NMe_2)Ph$ (**2f**)	4-NO_2Ph	Me	92[b]
9	$S(O)(NMe_2)Ph$ (**2f**)	4-NO_2Ph	Ph	71

[a] Conversion of aldehyde to γ-lactone as determined by GC-MS analysis of the crude. [b] dr = 60:40.



Scheme 2. Proposed reaction mechanism.

Surprisingly, preliminary studies determined that an unexpected 3,4-disubstituted regioisomer of the γ-lactone, **5**, 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 2). The connectivity found in lactone **5a** was revealed by examining the ^{1}H NMR signals for protons attached to C4 and C5. These were found at 4-5 ppm. Protons bonded to C4 in regioisomer **C** would not be expected to give signals at 4-5 ppm, but rather at *ca*. 2.5-3 ppm. The regioselectivity for **5** was confirmed by X-ray crystallographic analysis of **5d**.[7]

For all entries in Table 1, the aldehyde **3** was added slowly to the ylide **2a**-**2f** at –78 °C, and then the ketene **4** 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 higher temperatures (e.g. –30 °C) led to poor conversion to γ-lactone (<20%). The use of bases other than *n*-BuLi generally led to poorer yields of lactone **5**, with the notable exception being for **5c** where NaHMDS proved to be superior (Table 2). A variety of metal salt additives were also investigated for transmetallation in an effort to elevate the yield/conversion of **5**, but only $MgCl_2$ and CuI were found to give superior results to using *n*-BuLi without an additive, and indeed only for select examples (**5i** and **5za**, see Reaction scope and Table 2).[8] Tetrafluoroborate (BF_4^-), was used as a non-nucleophilic counterion for reactions involving sulfoxonium salt **1f**/ylide **2f** in order to minimize side reactions with ketenes (e.g., by avoiding iodide as a counterion).

The formation of product **5** rather than regioisomer **C** was rationalized in terms of the reaction mechanism presented in Scheme 2. Addition of Ylide **2f** to aldehyde **3** provides betaine **A**.[11,12] Nucleophilic addition of the alkoxide of betaine **A** to the less sterically hindered side of ketene **4** provides stereoselective access to enolate **B** (as the *E*-isomer for M = Li). Cyclization of enolate **B** at this point would provide γ-lactone regioisomer **C**. However, formation of γ-lactone regioisomer **C** was never observed during these studies, presumably due to steric interactions between the enolate substituents (R^2, R^3) and the sulfinamide leaving group. Instead, cyclization of enolate **B** to give six-membered sulfurane oxide **D** occurs faster than

formation of lactone **C**. Extensive studies by Martin's group and others have demonstrated that cyclic sulfurane oxides, including optically active examples, can be formed.[13,14] Sulfurane oxide anion **E** would then be generated through deprotonation of **D** by a base (e.g. ylide **2f**), which would subsequently undergo E1cB elimination to give enolate **F**.[15] We surmise that enolate **F** undergoes equilibration to the thermodynamically more stable *E*-enolate geometry under the reaction conditions, with final geometry as depicted in Scheme 2. Enolate **F** would then undergo a [3,3]-sigmatropic rearrangement in stereoselective fashion, through a chair-like transition state, to afford carboxylate **G**. The latter rearrangement in some ways resembles Marino's work on the synthesis of thio-substituted γ-lactones from vinyl sulfoxides and dichloroketene.[16,17] Protonation of **G** gives **H**, which undergoes an intramolecular S_N2 to provide γ-lactone **5** and sulfinamide leaving group **6**.

Reaction scope. The substrate scope of the reaction was then investigated with respect to variation of aldehyde/ketone, ketene, and sulfoxonium ylide substitution pattern (Table 2: 30 examples investigated).

The methodology was found to be versatile enough to tolerate disubstituted ketenes of quite diverse reactivity. Alkylarylketenes, diphenylketene, and dimethylketene worked very well to moderately well (e.g. **5a**, **5d**, **5o**, **5t** and **5y**). *c*-Hexylmethylketene, however, performed poorly only providing γ-lactone in *ca*. 5% yield. The ketenes in all cases were pre-prepared and purified (where possible) prior to being added to the reaction.[18] In general, best yields of γ-lactone were obtained with aromatic aldehydes (≥50% for 13 examples, up to 82%).[8] Yields with aliphatic aldehydes were more modest (32-39%), unless $MgCl_2$ was used as an additive (e.g. increase of yield from 32% to 93% for **5i**). We surmise that the role of $MgCl_2$ is to activate aliphatic aldehydes or stabilize formation of betaine **A** or, alternatively, to enable greater organization through chelation in the transition state for [3,3]-sigmatropic rearrangement of **F** to **G** (Scheme 2). However, with aromatic aldehydes $MgCl_2$ did not provide any advantage and so in most substrate investigations, the simple system of *n*-BuLi as base (without additive) was found to be optimal. The generally lower isolated yields for aliphatic aldehyde-derived lactones may be attributed to incomplete conversion in betaine **A** formation due to lower reactivity of sterically hindered *i*-Pr-substituted aldehyde examined, and, additionally, the relatively higher energy barrier to intermediate **F** undergoing [3,3]-sigmatropic rearrangement (Scheme 2).[8]

Me- and Ph-substituted aminosulfoxonium ylides (**2g** and **2h**) were also investigated with mixed results (**5zb**-**5ze**). While aminosulfoxonium ethylide **2g** provided moderate yield and diastereoselectivity in reaction with 4-NO_2PhCHO and ethylphenylketene (**5zb**), reaction with less reactive aldehydes, isobutyraldehyde and 2-naphthaldehyde, proved less successful with no γ-lactone being formed (**5zc** and **5zd**). Reactions involving aminosulfoxonium benzylide **2h** also proved fruitless (**5ze**).

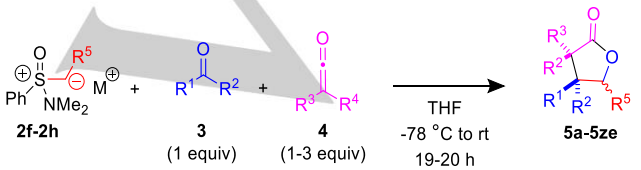
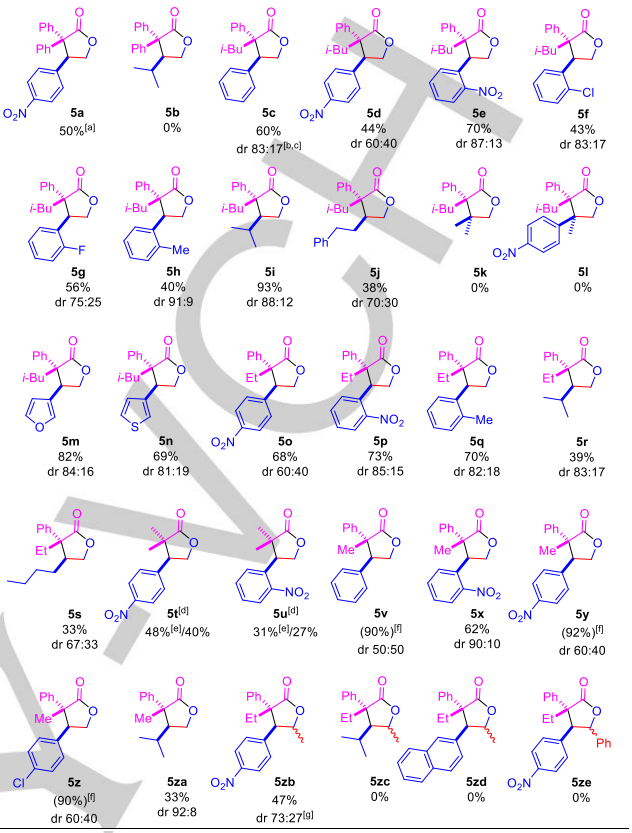


Table 2. Scope of γ-lactone synthesis.



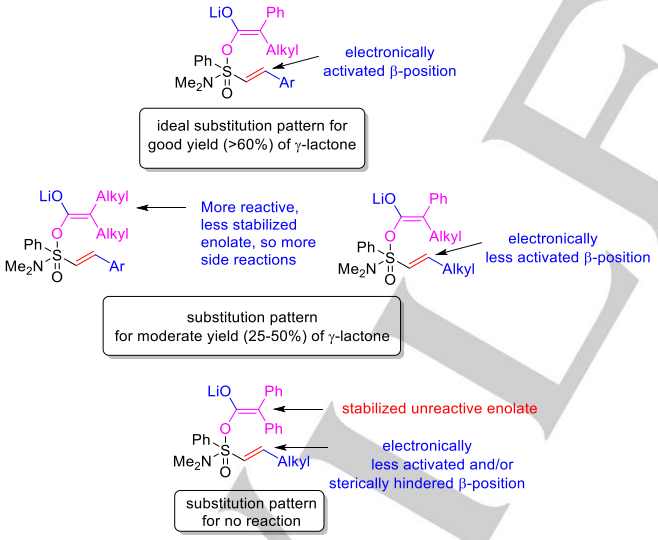
[a] Isolated yield for both diastereomers of **5**. [b] dr determined by GC-MS analysis of crude **5**. [c] **5c**: base = NaHMDS (M^+ = Na); **5i**: base = *n*-BuLi, salt additive = $MgCl_2$ (M^+ = MgCl); **5za**: base = *n*-BuLi, salt additive = CuI (M^+ = Cu); For all other examples: base = *n*-BuLi (M^+ = Li); [d] 3 equiv. of dimethylketene used. 1 equiv. of ketene used for all other examples. [e] Prepared using (*S*)-**2f**.[19] [f] Conversion of **3** to **5** as determined by GC-MS analysis. [g] major diastereomer: Σ of all other diasteromers.

Reaction between TMS-ketene with betaine, derived from aminosulfoxonium methylide and 2-NO_2PhCHO, was also investigated but provided no desired product. Clear methodology limitations were identified with regards to catering for monosubstituted ketenes, substituted sulfoxonium salts (R^5 = Me, Ph), and ketones (Table 2).

Good diastereoselectivity (dr ≥81:19, up to 92:8) was generally found for *ortho*-substituted aromatic aldehydes (**5e**, **5f**, **5h**, **5p**, **5q**, **5x**), lactones derived from PhCHO and heteroaromatic aldehydes (**5c**, **5m**, **5n**), and the α-branched aliphatic aldehyde, isobutyraldehyde (**5i**, **5r**, **5za**) (Table 2). A surprising exception was found for 2-$MeOC_6H_4CHO$, where the lactone product was obtained with moderate conversion (60%) and modest diastereoselectivity (dr 67:33). The low stereoselectivity was ascribed to a change in the elimination step (**D** to **F**, Scheme 2), whereby **F** is obtained as a mixture of *E*/*Z*-vinyl sulfurane oxide isomers due to a competing less stereoselective E1 process (as a consequence of the presence of the carbocation-stabilizing MeOAr-electron donating group at the β-position). Generally, poor to modest diastereoselectivity was observed for examples derived from 4-$NO_2C_6H_4CHO$ (**5d**, **5o**, **5y**) and aliphatic aldehydes lacking α-branching (**5j** and **5s**). Formation of the *trans*-isomer (*anti*-isomer, with both highest priority substituents at stereogenic centers on opposite sides of γ-lactone ring) as the

major diastereomer, was confirmed by X-ray crystallographic analysis of the major diastereomer of **5d** as previously described.[8a]

Substrate scope rationale. Higher yields with aromatic aldehydes can be attributed to the more reactive intermediate **F** that is formed when an aromatic substituent is present at the *β*-position of the *α,β*-unsaturated sulfurane oxide moiety of intermediate **F** (Scheme 3, top example). The latter substitution accelerates the [3,3]-sigmatropic rearrangement rather than competing intermolecular side reactions, such as aldol reactions between the enolate intermediate **F** and unreacted aldehyde **3**.[20] However, when an aliphatic aldehyde is utilized, a less reactive intermediate **F** is formed, due to the presence of the aliphatic substituent at the *β*-position of the *α,β*-unsaturated sulfurane oxide intermediate **F** (Scheme 3, middle example). This substitution causes a relatively slower [3,3]-sigmatropic rearrangement, leading to an increase in competing intermolecular side reactions. As a result, modest yields (32-39%) were obtained with aliphatic aldehydes, unless a metal salt additive was used (Table 2). Modest yields (**5t** and **5u**) were also obtained when dialkylketenes were employed, and this is attributed to the higher reactivity of the dialkyl-substituted enolate intermediate, leading to aldol side reactions in addition to [3,3]-sigmatropic rearrangement. A clear limitation of the methodology was found when diphenylketene was examined in a reaction with isobutyraldehyde (**5b**). No *γ*-lactone product **5b** was formed and this is due to the diphenyl-substituted enolate in intermediate **F** being too stabilized, in combination with the *α,β*-unsaturated sulfurane oxide of **F** lacking sufficient electrophilicity at the *β*-position (Scheme 3, lowest example).



Scheme 3. γ-Lactone yield rationale: rearrangement of Intermediate **F** for various substitution patterns.

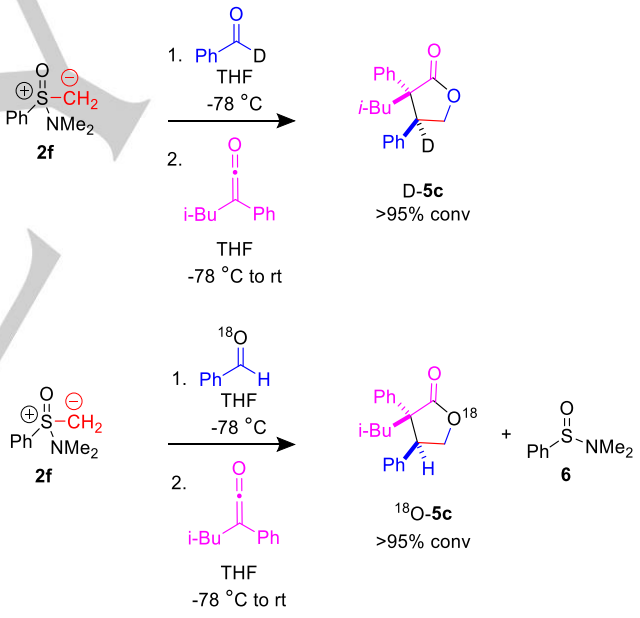
Reaction Mechanism. Having explored the substrate scope of the reaction methodology, we then proceeded to probe the proposed mechanism for the reaction (Scheme 2).[8] Labeling experiments were conducted to shed more light on how the molecules were undergoing rearrangement, and rule out alternative processes.

Deuterium labeling experiment

When deuterium-labeled benzaldehyde (PhCDO) was used as a substrate in reaction with **2f** and isobutylphenylketene, D-**5c** was obtained in >95% conversion (Scheme 4). Analysis of the integration of the lactone ring protons of D-**5c** by ^{1}H NMR showed that the signal corresponding to the benzylic proton (formerly aldehyde proton) at C4 was missing; Deuterium had been incorporated at the C4 position (see SI spectra). In addition, the splitting patterns for the signals at 4.55 ppm and 4.32 ppm changed from a double doublet and triplet in **5c** to a pair of doublets in D-**5c**. This experiment confirmed that the reaction mechanism involves a rearrangement as the aldehyde O-atom was no longer connected to C4 bearing D.

^{18}O labeled aldehyde experiment

Next, the possibility of the oxygen on the sulfoxonium ylide being incorporated into the product was examined. ^{18}O-labeled benzaldehyde (20% labeled with ^{18}O) was investigated as a substrate for the multicomponent reaction (Scheme 4). ^{18}O was found by GC-MS analysis to be incorporated into the lactone product **5c** (rather than into sulfinamide byproduct **6**) with the same relative incorporation as the starting material, thus ruling out incorporation of the oxygen from the sulfoxonium ylide, e.g. through involvement of the sulfoxonium oxygen as a nucleophile in the reaction mechanism (Schemes 2 and 4).



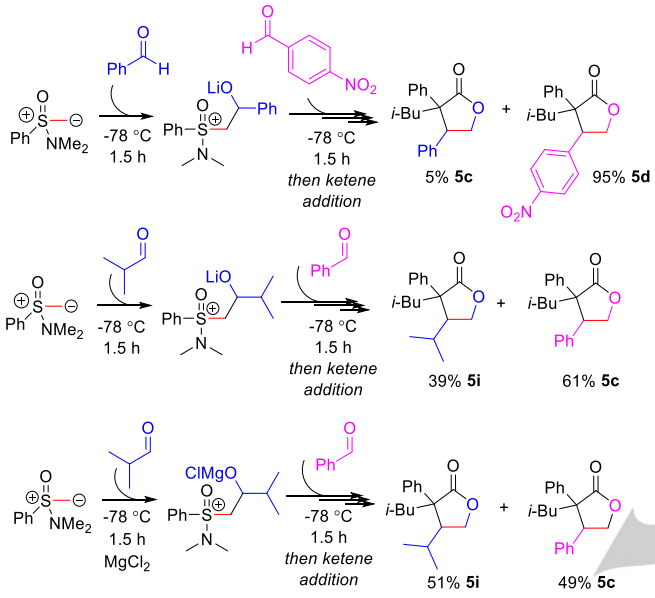
Scheme 4. Labeling experiments.

Crossover experiments

To test the reversibility of the reaction an experiment was carried out where, after betaine was allowed to form from PhCHO and **2f** for 1.5 h, another more reactive aldehyde (4-$NO_2C_6H_4CHO$) was added, followed by isobutylphenylketene (Scheme 5). This resulted in a product mixture of 95% lactone **5d**, derived from 4-$NO_2C_6H_4CHO$, and 5% **5c**, derived from PhCHO, indicating that betaine/oxathietane generation is reversible (Scheme 5).

Metal salt additives (e.g. $MgCl_2$) may provide an option for the activation of unreactive aldehydes and stabilization of intermediates. To understand this qualitatively, a similar experiment to above was carried out using less reactive

aldehydes *i*-PrCHO and PhCHO. The control experiment showed that the product mixture from this crossover experiment afforded 39% lactone **5i** (from *i*-PrCHO), and 61% **5c** (from PhCHO) (Scheme 5). Next, the same experiment was repeated but with $MgCl_2$ (1 equiv.) as additive in the reaction. This experiment provided a product mixture of 51% lactone **5i** (from *i*-PrCHO) and 49% **5c** (from PhCHO), demonstrating that betaine formation is less reversible in the presence of the Lewis acid (Scheme 5).

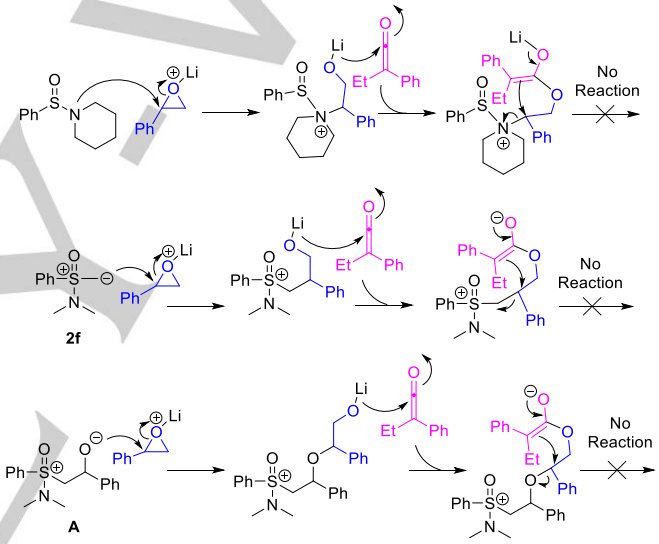


Scheme 5. Cross-over experiments (isobutylphenylketene was added after second aldehyde addition in all cases, as per general procedure A).

Control experiments

To test the mechanism further we carried out a number of control reactions involving an epoxide as a potential intermediate in order to determine whether it was relevant. As the Johnson-Corey-Chaykovsky reaction typically produces epoxide as the major product, we investigated whether styrene oxide would undergo reaction with ethylphenylketene to provide γ-lactone **5**.[9,21] If that occurred, then the regioselectivity in γ-lactone formation (product **5** rather **C**, Schemes 1 and 2) might be explained in terms of the regioselectivity of epoxide ring-opening, albeit an unexpected sense of regioselectivity (*attack at the more substituted carbon*, Scheme 6). Interestingly, Baba and co-workers had observed such regioselectivity in the reaction of epoxides with ketenes under Ph_4SbI catalysis.[21a] An experiment was carried out to test if the sulfinamide leaving group could add to lithium tetrafluoroborate-activated epoxide. A commercially available analogue, 1-(phenylsulfinyl)piperidine, was used as the nucleophile. If the sulfinamide was successful in ring-opening the epoxide, subsequently added ethylphenylketene would intercept the betaine, and γ-lactone would ultimately be formed (Scheme 6). However, no reaction was observed and therefore reaction of sulfinamide with epoxide (or indeed with ketene first) was ruled out as a possible step in γ-lactone formation. Direct reaction between the epoxide and the ketene could also be ruled out as a mechanism for γ-lactone formation.[21b]

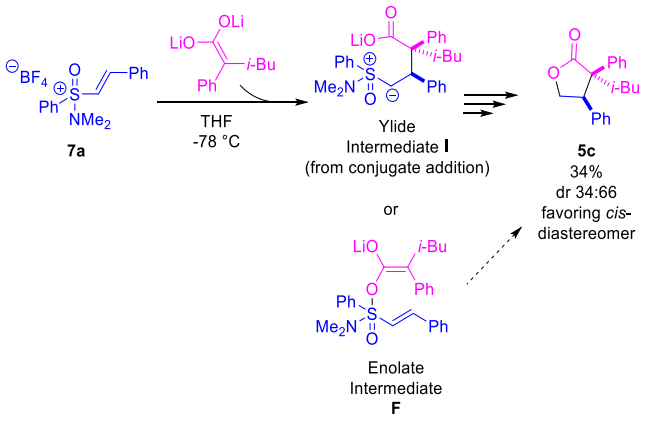
As betaine formation is reversible (see crossover experiments), the γ-lactone-forming reaction could be generating epoxide along with equilibrium quantities of ylide (Scheme 6). The ylide could ring-open the epoxide, followed by reaction with ketene to give the γ-lactone product. This idea was tested by generating the ylide **2f** and adding epoxide followed by ketene under standard conditions. However, once again, no reaction occurred. Another possible explanation for the observed regioselectivity was proposed as follows: if epoxide is forming from betaine, excess betaine in the solution could act as a catalyst which opens the epoxide to give a new zwitterion that would then react with the ketene to produce γ-lactone and regenerate betaine catalyst through cyclization (Scheme 6). To test this proposal, the betaine was generated as per general procedure A, and then one equivalent of styrene oxide and ethylphenylketene was added. GC-MS analysis of the reaction mixture revealed a complex mixture which did not include the desired γ-lactone product.



Scheme 6. Control experiments to test mechanistic scenarios for formation of γ-lactone from epoxide intermediate (only one regioisomer from epoxide opening shown).

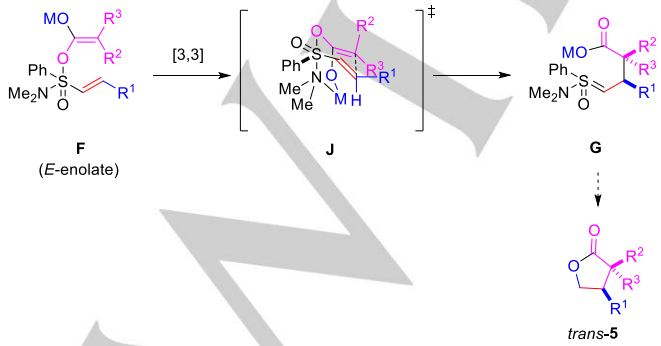
Finally, an attempt was made to replicate the proposed reaction mechanism (Scheme 2) by independently generating the putative enolate intermediate **F**, which precedes the [3,3]-sigmatropic rearrangement. An *α*,*β*-unsaturated sulfoxonium salt **7a** was subjected to reaction with a lithium enediolate (Scheme 7).[22] Previously, the groups of Johnson and Gais had independently reported synthesis protocols for a variety of *α*,*β*-unsaturated sulfoxonium salts.[23,24] By adding *n*-BuLi (2 equiv.) to 4-methyl-2-phenylpentanoic acid, a homogeneous solution of lithium enediolate was easily accessed. Slow addition of the lithium enediolate solution to the salt **7a** suspension in THF at low temperature (–78 °C) allowed for conversion to the lactone product **5c** in 34% yield, but with the *cis*-diastereomer favored (as determined by relative retention time using GC-MS analysis, see SI). While the same γ-lactone structural connectivity (i.e. regioisomer **5**) was observed for the product (**5c**) formed, the differing sense (*cis* instead of *trans*) and magnitude of diastereoselectivity (dr 34:66 vs 83:17 for *trans* example **5c** in

Table 2) does suggest that the lithium enediolate reaction goes through a different intermediate (i.e. ylide **I** formed through conjugate addition) to that of lactones formed using the method reported in this paper (Scheme 7).[22]



Scheme 7. Reaction of lithium enediolate with vinyl sulfoxonium salt **7a**.

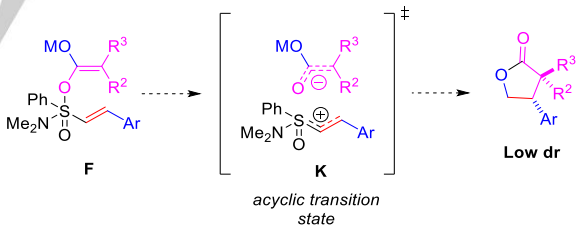
Diastereoselectivity rationale. Diastereoselectivity in γ-lactone formation is explained by invoking a [3,3]-sigmatropic rearrangement of enolate **F** as the key stereodetermining step (Scheme 8).[16] Enolate **F** is expected to adopt a six-membered chair-like transition state, where the more sterically bulky substituents (R^1 and R^3) prefer to occupy pseudoequatorial positions in the chair (Scheme 8).[25] We hypothesise that the –NMe_2 and O-enolate substituents of intermediate **F** occupy apical positions at sulfur (in a trigonal bipyramidal geometry) in transition state **J** (Scheme 8). Such an arrangement is consistent with those previously reported for cyclic sulfurane oxides bearing electronegative substituents.[13-15] Chelation of the enolate O-atom (derived from aldehyde) and the N-atom of the -NMe_2 group by the metal (M = Li or MgCl) would provide important transition state organization for the achievement of high diastereoselectivity (Scheme 8). [3,3]-sigmatropic rearrangement of intermediate **F**, via transition state **J**, where the enolate is predominately in the *E*-isomeric form, results in the formation of the *trans*-diastereomer of the γ-lactone as the major isomer.



Scheme 8. Rationale for diastereoselectivity.

Highest levels of diastereoselectivity were observed when a sterically demanding substituent (e.g., R^1 = *i*-Pr, 2-MePh, 2-NO_2Ph) was located at the β-position of the α,β-unsaturated sulfurane oxide intermediate **F** (e.g. for **5h**, **5x**, **5za**). This outcome may be explained by an increased preference for the R^1 substituent to adopt a pseudoequatorial position, in order to minimize 1,3-diaxial interactions with the -NMe_2 group (and enolate O).

Lower levels of diastereoselectivity (dr 50:50-70:30) were often observed for those reactions involving 4-$NO_2C_6H_4CHO$ and unbranched aliphatic aldehydes. For 4-$NO_2C_6H_4CHO$, poor to moderate diastereoselectivity may be explained by postulating a more reactive intermediate (**F**), with a corresponding earlier and less organized transition state, and with a lower energy barrier to rearrangement. As a result, there would be lower discrimination between competing diastereomeric transition states, and hence lower diastereoselectivity. Additionally, if Intermediate **F** reacts through an acyclic transition state **K**, containing charge separation, that resembles the reaction of an enediolate and an α,β-unsaturated sulfoxonium salt, low diastereoselectivity is expected (Scheme 9).[22] Indeed, analyzing results from the addition of tetrasubstituted enediolates to vinyl sulfoxonium salts (where Ar = Ph) showed that a lower dr (e.g. dr 34:66 for **5c**, Scheme 7) was indeed observed, suggesting that if the [3,3]-rearrangement step proceeded through an enediolate/vinyl sulfoxonium-like transition state **K** that lower diastereoselectivity would be observed. Lower diastereoselectivity associated with unbranched aliphatic aldehydes may be attributed to reduced steric interactions in the transition state **J** (Scheme 8), and hence increased competition from alternative transition states, with R^1 or R^3 (larger substituent) in pseudoaxial position of chair-like transition state, or alternatively due to a competing boat transition state.



Scheme 9. Rationale for low diastereoselectivity.

Conclusions

In conclusion, we have developed a versatile reaction that provides diastereoselective access to γ-lactones, through the reaction of sulfoxonium ylides, aldehydes and disubstituted ketenes. Interesting features of the method are that it affords direct access to *trans*-γ-lactones, through an unusual ketene-directed extension to the Johnson-Corey-Chaykovsky reaction, in good yields (up to 93%), and with good diastereoselectivity (12 examples with dr ≥80:20, up to 92:8). Mechanistic studies, involving labeling, crossover and control experiments, strongly suggest that the reaction does not involve an epoxide intermediate, but does involve reversible betaine formation, enolate formation, and a [3,3]-sigmatropic rearrangement, with diastereoselectivity determined in the latter step.

Experimental Section

General

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere technique unless otherwise stated. THF was dried using a sodium/benzophenone ketyl still, and *N*,*N*-dimethylethylamine was distilled from potassium hydroxide under nitrogen.[26] 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 **1f,** (dimethylamino)ethylphenyl oxosulfonium fluoroborate **1g** and (dimethylamino)benzylphenyl oxosulfonium fluoroborate **1h** were synthesized according to literature procedures.[23] Diphenylketene, methylphenylketene, ethylphenylketene, and isobutylphenylketene were prepared through amine-mediated dehydrohalogenation, while TMS-ketene was prepared from ethylethynyl ether.[18] Dimethylketene was prepared through zinc-mediated dehalogenation of 2-bromo-2-methylpropionyl bromide.[18d]

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.

Diastereomeric ratios for *γ*-lactones **5** were determined by GC-MS analysis of the crude product, and corroborated by ^{1}H NMR analysis in each case. Products **5c**-**5h**, **5l**-**5n**, **5p**-**5r**, **5t**, **5v**-**5z**, and **5za** were prepared and characterized as previously reported.[8]

General procedure A for preparation of *γ*-lactones: (Dimethylamino)methylphenyl oxosulfonium fluoroborate **1f** (or **1g**) was placed under high vacuum for 0.5 h. After drying, the sulfoxonium salt **1f** (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 **5c** 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 minutes for dialkylketene). After stirring 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 5i and 5za: (Dimethylamino)methylphenyl oxosulfonium fluoroborate **1f** was placed under high vacuum for 0.5 h. After drying, the sulfoxonium salt **1f** (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. Transmetallation was assumed complete after 15 minutes. 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 stirring 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.

4-(4-Nitrophenyl)-3,3-diphenyldihydrofuran-2(3H)-one (5a): Sulfoxonium salt **1f** (68 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol), 4-nitrobenzaldehyde (38 mg, 0.25 mmol), and diphenylketene (49 mg, 0.25 mmol) were added following general procedure A. After elution with 20% EtOAc/hexane, **5a** was isolated as a yellow solid (45 mg, 50%); IR (thin film): 1771, 1591 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS): δ 7.98-7.94 (m, 2H), 7.60-7.57 (m, 2H), 7.44-7.34 (m, 3H), 7.15-7.06 (m, 3H), 7.04-7.01 (m, 2H), 6.82-6.79 (m, 2H), 4.75-4.70 (m, 2H), 4.58-4.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 147.3, 144.9, 138.8, 138.2, 129.8, 129.4, 129.1, 128.5, 128.3, 128.2, 127.7, 123.6, 69.4, 62.2, 50.5; (M^++H) HRMS m/z calcd for $C_{22}H_{18}NO_4^+$: 360.1236; found: 360.1233.

3-Isobutyl-4-phenethyl-3-phenyldihydrofuran-2(3H)-one (5j): Sulfoxonium salt **1f** (68 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol), hydrocinnamaldehyde (40 mg, 0.25 mmol), and isobutylphenylketene (44 mg, 0.25 mmol) was added following general procedure A. After elution with 2% EtOAc/hexane, **5j** was isolated as a colorless oil (30 mg, 38%) with a dr = 70:30 as determined by GC-MS analysis of the crude product; R_f = 0.4 (EtOAc/hexane 1:9); IR (thin film): 1771 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the mixture of diastereomers: δ 7.35-7.03 (m, 20H), 4.41 (dd, *J* = 7.3 Hz, 8.9 Hz, 1H), 4.22 (dd, *J* = 6.6 Hz, 9.0 Hz, 1H), 4.07 (dd, *J* = 7.1 Hz, 9.0 Hz, 1H), 3.79 (t, *J* = 9.1 Hz, 1H), 2.66-2.42 (m, 6H), 1.98-1.71 (m, 4H), 1.70-1.57 (m, 4H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) for the mixture of diastereomers: δ 179.4, 179.2, 141.1, 141.0, 139.8, 137.6, 128.84, 128.8, 128.75, 128.7, 128.4, 128.3, 127.59, 127.56, 127.5, 127.3, 126.5, 126.47, 69.8, 69.3, 55.4, 54.2, 48.0, 43.6, 38.9, 38.9, 33.7, 30.6, 28.7, 25.4, 25.2, 24.64, 24.63, 24.3, 24.2; MS (EI 70eV): 322, 266, 161, 91 m/z; (M^++H) HRMS m/z calcd for $C_{22}H_{27}O_2^+$: 323.2011; found: 323.2009.

3-Ethyl-4-(4-nitrophenyl)-3-phenyldihydrofuran-2(3H)-one (5o): Sulfoxonium salt **1f** (68 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25

mmol), 4-nitrobutylaldehyde (38 mg, 0.25 mmol), and ethylphenylketene (37 mg, 0.25 mmol) was added following general procedure A. After elution with 20% EtOAc/hexane, **5o** was isolated as a white solid (50 mg, 68%) with a dr = 60:40 as determined by GC-MS analysis of the crude product; IR (thin film): 1770, 1520, 1347 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 8.33-8.20 (m, 2H), 7.45-7.30 (m, 7H), 4.54-4.46 (m, 2H), 3.99 (t, *J* = 6.0 Hz, 1H), 1.68-1.61 (m, 1H), 1.56-1.49 (m, 1H), 0.72 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major diastereomer: δ 177.9, 147.8, 144.7, 138.1, 129.4, 129.2, 128.1, 127.2, 124.1, 69.4, 56.4, 54.0, 26.1, 8.4; MS (EI 70eV): 311, 283, 238, 192, 146, 117, 103, 91, 77 m/z; $(M^+ + H)$ HRMS m/z calcd for $C_{18}H_{18}NO_4^+$: 312.1236; found: 312.1234.

4-Butyl-3-ethyl-3-phenyldihydrofuran-2(3H)-one (5s): Sulfoxonium salt **1f** (68 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol), valeraldehyde (22 mg, 0.25 mmol), and ethylphenylketene (37 mg, 0.25 mmol) was added following general procedure A. After elution with 1.5% EtOAc/hexane, **5s** was isolated as a colorless oil (20 mg, 33%) with a dr = 67:33 as determined by GC-MS analysis of the crude product; R_f = 0.4 (EtOAc/hexane 1:9); IR (thin film): 1767 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS) for the mixture of diastereomers: δ 7.39-7.16 (m, 10H), 4.40 (dd, *J* = 7.4 Hz, 9.0 Hz, 1H), 4.28 (dd, *J* = 6.9 Hz, 9.0 Hz, 1H), 4.00 (dd, *J* = 7.4 Hz, 9.0 Hz, 1H), 3.77 (t, *J* = 9.4 Hz, 1H), 2.62-2.51 (m, 2H), 2.16-1.85 (m, 4H), 1.59-1.10 (m, 12H), 1.01 (t, *J*= 7.3, 3H), 0.90-0.85 (m, 6H), 0.81 (t, *J*=7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the mixture of diastereomers: δ 180.1, 179.5, 139.8, 137.2, 128.8, 128.7, 127.6, 127.4, 127.34, 127.28, 70.1, 69.9, 55.5, 54.7, 48.1, 44.4, 29.8, 29.7, 28.5, 28.3, 26.5, 23.7, 23.0, 22.9, 14.1, 14.0, 9.2, 9.0; MS (EI 70eV): 246, 218, 154, 117, 91 m/z; $(M^+ + H)$ HRMS m/z calcd for $C_{16}H_{23}O_2^+$: 247.1698; found: 247.1690.

3,3-Dimethyl-4-(2-nitrophenyl)dihydrofuran-2(3H)-one (5u): Sulfoxonium salt (*S*)-**1f** (68 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol), 2-nitrobenzaldehyde (38 mg, 0.25 mmol) and dimethylketene (56 mg, 0.80 mmol) were added following general procedure A. After elution with 5% EtOAc/hexane, **5u** was isolated as a white solid (18 mg, 31%); R_f = 0.4 (EtOAc/hexane 1:4); IR (thin film): 1767, 1485, 1349 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS): δ 7.88-7.86 (m, 1H), 7.65-7.60 (m, 1H), 7.47-7.41 (m, 2H), 4.69 (dd, *J* = 6.8 Hz, 10.1 Hz, 1H), 4.48 (dd, *J* = 2.2 Hz, 6.8 Hz, 1H), 4.03 (dd, *J* = 2.2 Hz, 6.8 Hz, 1H), 1.49 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.4, 150.1, 135.1, 133.9, 128.7, 128.1, 125.0, 70.8, 46.3, 44.7, 25.8, 20.4; MS(EI 70eV): 206, 160, 132, 120, 104, 91, 77 m/z; $(M^+ + H)$ HRMS m/z calcd for $C_{12}H_{14}NO_4^+$: 236.0923; found: 236.0928.

3-Ethyl-5-methyl-4-(4-nitrophenyl)-3-phenyldihydrofuran-2(3H)-one (5zb): Sulfoxonium salt **1g** (72 mg, 0.25 mmol) was suspended in THF (1.5 mL). *n*-Butyllithium (2.5 M in hexane, 0.1 mL, 0.25 mmol), 4-nitrobenzaldehyde (38 mg, 0.25 mmol) and ethylphenylketene (36.5 mg, 0.25 mmol) were added following general procedure A. After elution with an EtOAc/hexane system, **5zb** was isolated as an oil (38 mg, 47%) with a dr = 73:27 as determined by GC-MS analysis of the crude product; IR (thin film): 1761, 1519, 1346 cm^{-1}; ^1H (400 MHz, $CDCl_3$, TMS): δ 7.94-7.91 (m, 2H), 7.42-7.40 (d, *J* = 8 Hz, 2H), 7.12-6.99 (m, 5H), 5.18 (*app* quint, *J* = 6.5 Hz, 1H), 3.84 (d, *J* = 5.7 Hz, 1H), 2.44-2.37 (m, 1H), 2.21-2.14 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 146.9, 144.8, 137.5, 130.6, 128.3, 128.2, 126.8, 123.4, 75.2, 59.1, 57.3, 33.6, 17.4, 9.0; MS (EI 70eV): 325, 253, 117, 91, 77 m/z; $(M + H)^+$ HRMS m/z calcd for $C_{12}H_{14}NO_4^+$: 326.1387; found: 326.1395.

Determination of relative and absolute stereochemistry: A sample of the major diastereomer of **5d** was crystallized from hexane and acetone to provide crystals suitable for X-ray crystallographic analysis, as previously described.[8a] The crystal structure showed the *trans*-relative stereochemistry of the major diastereomer of *γ*-lactone **5d**. The relative stereochemistry of *γ*-lactones **5a**-**5ze** was assigned to be *trans* by analogy.

Mechanistic experiments:

Synthesis of D-5c from PhCDO. Following general procedure A, D-**5c** was synthesized using sulfoxonium salt **1f**, *α*-D-benzaldehyde (98%), and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with H_2O (2 × 10 mL). The crude product was analyzed by GC-MS prior to purification and it was determined that the reaction proceeded with a conversion of >95% and dr = 76:24. The crude was purified through a plug of neutral silica eluting with 1.5% EtOAc/hexane, and D-**5c** was isolated as a colorless oil; ^1H (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 7.19-7.12 (m, 6H), 6.87-6.83 (m, 2H), 6.74-6.70 (m, 2H), 4.56 (d, *J* = 8.7 Hz, 1H), 4.32 (d, *J* = 8.7 Hz, 1H), 2.07-2.00 (m, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz); MS (EI 70eV): 295, 252, 239, 194, 131, 105, 77 m/z.

Synthesis of ^{18}O-5c from PhCH^{18}O. Following general procedure A, ^{18}O-**5c** was synthesized using sulfoxonium salt **1f**, ^{18}O labeled benzaldehyde (20% ^{18}O)[27], and isobutylphenylketene. The crude product solution was diluted with ether (10 mL) and washed with of H_2O (2 × 10 mL). The crude product was analyzed by GC-MS and found to contain ^{18}O-**5c** with the same relative incorporation of ^{18}O as the labeled benzaldehyde starting material (20%); MS (EI 70eV) for ^{18}O-**5c**: 296 m/z

Crossover experiment of benzaldehyde and 4-nitro-benzaldehyde. The reaction was performed using sulfoxonium salt **1f** (0.25 mmol), *n*-BuLi (0.25 mmol) as base, benzaldehyde (0.25 mmol), 4-nitrobenzaldehyde (0.25 mmol), and isobutylphenylketene (0.25 mmol). After addition of *n*-BuLi to sulfoxonium salt **1f** 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. Next, 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 via syringe pump over 1 h. 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 combined organics were dried with $MgSO_4$ and filtered. 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% **5c** (dr = 86:14) and *ca*. 95% **5d** (dr = 62:38): MS (EI 70 eV) for **5c**: 294, 238, 193, 131, 103, 77 *m/z*; MS (EI 70 eV) for **5d**: 339, 296, 283, 192, 131, 103, 77 *m/z*.

Crossover experiment of isobutyraldehyde and benzaldehyde. The reaction was performed using sulfoxonium salt **1f** (0.25 mmol), *n*-BuLi (0.25 mmol) as base, isobutyraldehyde (0.25 mmol), benzaldehyde (0.25 mmol), and isobutylphenylketene (0.25 mmol). After addition of *n*-BuLi to sulfoxonium salt **1f** in THF and 45 min of stirring at −78 °C,

isobutyraldehyde was added dropwise, and the reaction was stirred for 1.5 h at −78 °C. Then benzaldehyde was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, a THF solution of isobutylphenylketene was added via syringe pump over 1 h. 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 combined organics were dried with $MgSO_4$ and filtered. The crude product was analyzed by GC−MS, and it was determined that the reaction product was composed of *ca*. 39% **5i** and *ca*. 61% **5c**.

Crossover experiment of isobutyraldehyde, benzaldehyde, and $MgCl_2$. The reaction was performed using sulfoxonium salt **1f** (0.25 mmol), *n*-BuLi (0.25 mmol) as base, isobutyraldehyde (0.25 mmol), benzaldehyde (0.25 mmol), magnesium chloride (0.25 mmol), and isobutylphenylketene (0.25 mmol). After addition of *n*-BuLi to sulfoxonium salt **1f** in THF and 45 min of stirring at −78 °C, $MgCl_2$ was added and the reaction was stirred for 15 min. Isobutyraldehyde was added dropwise, and the reaction was stirred for 1.5 h at −78 °C. Then PhCHO was added dropwise, and the reaction was stirred for another 1.5 h at −78 °C. Finally, a THF solution of isobutylphenylketene was added via syringe pump over 1 h. 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 combined organics were dried with $MgSO_4$ and filtered. The crude product was analyzed by GC−MS, and it was determined that the reaction product was composed of *ca*. 51% **5i** and *ca*. 49% **5c**.

Sulfinamide-catalyzed addition of epoxide to ketene. Styrene oxide (0.25 mmol) was added to a solution of 1-(phenyl sulfinyl)piperidine (0.25 mmol) and lithium tetrafluoroborate (0.25 mmol) in THF followed by syringe pump addition of ethylphenylketene (0.25 mmol) over 1 h at –78 °C, and the reaction was allowed to warm to rt overnight. GC-MS analysis of the crude showed that no lactone was formed.

Ylide-catalyzed addition of epoxide to ketene. *n*-BuLi (0.05 mmol) was added to sulfoxonium salt **1f** (0.05 mmol) in THF at –78 °C and stirred for 45 min. Styrene oxide (0.25 mmol) was added in one portion followed by syringe pump addition of ethylphenylketene (0.25 mmol) over 1 h at –78 °C, and the reaction was allowed to warm to rt overnight. GC-MS analysis of the crude showed that no lactone was formed.

Betaine-catalyzed addition of epoxide to ketene. *n*-BuLi (0.05 mmol) was added to sulfoxonium salt **1f** (0.05 mmol) in THF at –78 °C and stirred for 45 min. Benzaldehyde (0.05 mmol) was added and the reaction was stirred for 1.5 h to generate betaine. Styrene oxide (0.25 mmol) was added in one portion, followed by syringe pump addition of ethylphenylketene (0.25 mmol) over 1 h at –78 °C, and the reaction was allowed to warm to rt overnight. GC-MS analysis of the crude showed that no lactone was formed.

Synthesis of 5c from lithium enediolate and vinyl sulfoxonium salt 7a. To a suspension of 4-methyl-2-phenylpentanoic acid (1 equiv.) in THF at –78 °C was added *n*-BuLi (2 equiv.). After 2 h of stirring, lithium enediolate[22] was added via syringe pump over 1 h to vinyl sulfoxonium salt **7a** [23,24] (1 equiv.) in THF at –78 °C. The reaction was warmed to room temperature overnight and worked up as per general procedure A. **5c** was isolated in 34% yield, dr = 34:66, with the *cis*-isomer favored as major diastereomer, as determined by relative retention times on GC-MS analysis of the crude product mixture (see SI spectra).

Acknowledgments

Support has been provided by the National Science Foundation (US): Grant No. CHE-1463728 to N.J.K.

Keywords: lactones • cumulenes • ylides • betaines • diastereoselectivity

[1] (a) M. Seitz, O. Reiser, *Curr. Opinion in Chem. Biol.* **2005**, *9*, 285-292; (b) A. Janecka, A. Wyrębska, K. Gach, J. Fichna, T. Janecki, *Drug Discov. Today* **2012**, *17*, 561-572; (c) H. M. R. Hoffman, J. Rabe, *Angew. Chem.* **1985**, *97*, 96-112; *Angew. Chem., Int. Ed.* **1985**, *24*, 94-110; (d) S. S. C. Koch, A. R. Chamberlain, In *Studies in Natural Products Chemistry, Vol. 16.* Atta-ur-Rahman, Ed.; Elsevier Science; 1995, p 687-725.

[2] (a) P. V. Ramachandran, D. Pratihar, H. Narayanan, G. Nair, M. Walters , S. Smith, M. T. Yip-Schneider, H. Wub, C. M. Schmidt, *Bioorg. & Med. Chem. Lett.* **2010**, *20*, 6620-6623; (b) P. V. Ramachandran, D. R. Nicponski, H. N. G. Nair, M. A. Helppi, P. D. Gagare, C. M. Schmidt, M. T. Yip-Schneider, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6911-6914.

[3] (a) P. de March; M. Figueredo, J. Font, J. Raya, *Org. Lett.* **2000**, *2*, 163-165; (b) A. K. Ghosh, L. Swanson, *J. Org. Chem.* **2003**, *68*, 9823-9826; (c) K. Chiyoda, J. Shimokawa, T. Fukuyama, *Angew. Chem.* **2012**, *124*, 2555-2558; *Angew. Chem. Int. Ed.* **2012**, *51*, 2505-2508.

[4] (a) S.-i. Fukuzawa, K. Seki, M. Tatsuzawa, K. Mutoh, *J. Am. Chem. Soc.* **1997**, *119*, 1482-1483; (b) P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1999,** *121,* 7708-7709; (c) S. Murahashi, S. Ono, Y. Imada, *Angew. Chem.* **2002**, *114*, 2472-2474; *Angew. Chem. Int. Ed.* **2002**, *41*, 2366-2368; (d) N. J. Kerrigan, P. C. Hutchison, T. D. Heightman, D. J. Procter, *Chem. Commun.* **2003**, 1402-1403; (e) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370-14371; (f) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331-6334; *Angew. Chem., Int. Ed.* **2004**, *43*, 6205-6208; (g) D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298-3300; (h) K. M. Steward, E. C. Gentry, J. S. Johnson, *J. Am. Chem. Soc.* **2012**, *134*, 7329-7332; (i) C. G. Goodman, M. M. Walker, J. S. Johnson, *J. Am. Chem. Soc.* **2015**, *137*, 122-125.

[5] D. J. Spielvogel, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 3500-3501.

[6] B. Mao, M. Fañanás-Mastral, B. L. Feringa *Chem. Rev.* **2017**, *117*, 10502-10566.

[7] (a) M. Mondal, S. Chen, N. Othman, K. A. Wheeler, N. J. Kerrigan, *J. Org. Chem.* **2015**, *80*, 5789-5794; (b) M. Mondal, K. A. Wheeler, N. J. Kerrigan, *Org. Lett.* **2016**, *18*, 4108-4111; (c) M. Mondal, M. Panda, N. W. Davis, V. McKee, N. J. Kerrigan, *Chem. Commun.* **2019**, *55*, 13558-13561; (d) M. Mondal, M. Panda, V. McKee, N. J. Kerrigan, *J. Org. Chem.* **2019**, *84*, 11983-11991; (e) A. D. Allen, T. T. Tidwell, *Arkivoc* **2016**, part (i), 415-490.

[8] (a) M. Mondal, H.-J. Ho, N. J. Peraino, M. A. Gary, K. A. Wheeler, N. J. Kerrigan, *J. Org. Chem.* **2013**, *78*, 4587-4593; (b) N. J. Peraino, H.-J. Ho, M. Mondal, N. J. Kerrigan, *Tetrahedron Lett.* **2014**, *55*, 4260-4263.

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

[10] (a) V. K. Aggarwal, J. N. Harvey, R. Robiette, *Angew. Chem.* **2005**, 117, 5604-5607; *Angew. Chem. Int. Ed.* **2005**, 44, 5468-5471; (b) V. K. Aggarwal, J. N. Harvey, J. Richardson, *J. Am. Chem. Soc.* **2002**, *124*, 5747-5756; (c) F. Volatron, O. Eisenstein, *J. Am. Chem. Soc.* **1984**, *106*, 6117-6119.

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

[12] J.-Y. Wu, Z.-B. Luo, L.-X. Dai, X.-L. Hou, *J. Org. Chem.* **2008**, *73*, 9137-9139.

[13] (a) J. C. Martin, E. F. Perozzi, *J. Am. Chem. Soc.* **1974**, *96*, 3155-3168; (b) J. C. Rongione, J. C. Martin, *J. Am. Chem. Soc.* **1990**, *112*, 1637-1638.
[14] J. Drabowicz, J. C. Martin, *Pure & Appl. Chem.* **1996**, *68*, 951-956.
[15] P. H. W. Lau, J. C. Martin, *J. Am. Chem. Soc.* **1977**, *99*, 5490-5491.
[16] J. P. Marino, M. Neisser, *J. Am. Chem. Soc.* **1981**, *103*, 7687-7689.
[17] D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701-8780.
[18] (a) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006-10007; (b) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176-6177; (c) A. D. Allen, L. M. Baigrie, L. Gong, T. T. Tidwell, *Can. J. Chem.* **1991**, *69*, 138-145; (d) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116,* 6518-6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358-6360; (e) R. A. Ruden, *J. Org. Chem.* **1974**, *39*, 3607-3608.
[19] J. Brandt, H.-J. Gais, *Tetrahedron: Asymmetry* **1997**, *6*, 909–912.
[20] D. P. Curran, Y.-G. Suh, *J. Am. Chem. Soc.* **1984**, *106*, 5002-5004.
[21] (a) M. Fujiwara, M. Imada, A. Baba, H. Matsuda, *J. Org. Chem.* **1988**, *53*, 5974-5977; (b) R. Oda, S. Muneimiya, M. Okano, *J. Org. Chem.* **1961**, 26, 1341-1343.
[22] (a) N. J. Peraino, K. A. Wheeler, N. J. Kerrigan, *Org. Lett.* **2015**, *17*, 1735-1737; (b) N. J. Peraino, S. H. Kaster, K. A. Wheeler, N. J. Kerrigan, *J. Org. Chem.* **2017**, *82*, 606-615.
[23] (a) C. R. Johnson, M. Haake, C. W. Schroeck, *J. Am. Chem. Soc.* **1970**, *92*, 6594-6598; (b) C. R. Johnson, C. W. Schroeck, *J. Am. Chem. Soc.* **1973**, *95*, 7418-7423; (c) C. R. Johnson, J. P. Lockard, E. R. Kennedy, *J. Org. Chem.* **1980**, *45*, 264-271; (d) M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull, *Angew. Chem.*, **2016**, 128, 7319-7323; *Angew. Chem. Int. Ed.*, **2016**, 55, 7203-7207; (e) A. Tota, M. Zenzola, S. Chawner, S. St John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Commun.* **2017**, *53*, 348-351; (f) M. Mondal, S. Chen, N. J. Kerrigan, *Molecules* **2018**, *23*, 738.
[24] H.-J. Gais, R. Hainz, H. Müller, P. Bruns, N. Giesen, G. Raabe, J. Runsink, S. Nienstedt, J. Decker, M. Schleusner, J. Hachtel, R. Loo, C.-W. Woo, P. Das, *Eur. J. Org. Che*m. **2000**, 3973-4009.
[25] Y. Chai, S.-p. Hong, H. A. Lindsay, C. McFarland, M. C. McIntosh, *Tetrahedron* **2002**, *58*, 2905-2928.
[26] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th Ed. Butterworth Heinemann, **2002**.
[27] M. Byrn, M. Calvin, *J. Am. Chem. Soc*. **1966**, *88*, 1916-1922.

Entry for the Table of Contents (Please choose one layout)

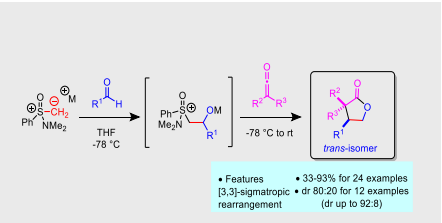
Layout 1:

FULL PAPER

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

FULL PAPER



The reaction of sulfoxonium ylides, aldehydes, and disubstituted ketenes provides access to γ-lactones in moderate to excellent yields, and with moderate to good diastereoselectivity favoring the *trans*-diastereomer (dr up to 92:8). A [3,3]-sigmatropic rearrangement is proposed to be the key mechanistic step.

Diastereoselectivity, lactones*

*Nicholas J. Peraino, Mukulesh Mondal, Han-Jen Ho, Antoine Beuque, Evan Viola, Melanie Gary, Kraig A. Wheeler and Nessan J. Kerrigan**

Page 1 – Page 10

Diastereoselective Synthesis of γ-Lactones through Reaction of Sulfoxonium ylides, Aldehydes and Ketenes: Substrate Scope and Mechanistic Studies