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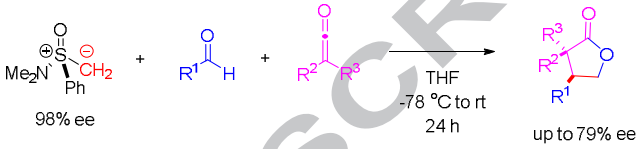

A method for the enantioselective synthesis of γ-lactones through the reaction of enantioenriched sulfoxonium ylides, aldehydes and ketenes was developed. Enantioenriched (98% ee) aminosulfoxonium ylide was subjected to reaction with a variety of aldehydes (both aromatic and aliphatic) and disubstituted ketenes, leading to the formation of α,β-substituted γ-lactones in moderate to very good diastereoselectivity (dr up to 95:5) and with enantiomeric excesses of up to 79% ee.

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Asymmetric Synthesis of γ-Lactones through Reaction of Sulfoxonium Ylides, Aldehydes and Ketenes

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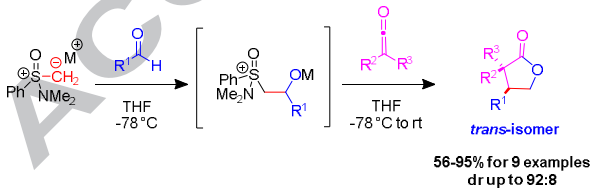
Abstract—A method for the enantioselective synthesis of γ-lactones through the reaction of enantioenriched sulfoxonium ylides, aldehydes and ketenes was developed. Enantioenriched (98% ee) aminosulfoxonium ylide was subjected to reaction with a variety of aldehydes (both aromatic and aliphatic) and disubstituted ketenes, leading to the formation of α,β-substituted γ-lactones in moderate to very good diastereoselectivity (dr up to 95:5) and with enantiomeric excesses of up to 79% ee. Best levels of enantioselectivity were observed in the reactions of enantioenriched aminosulfoxonium ylide with isobutyraldehyde and various alkylarylketenes.

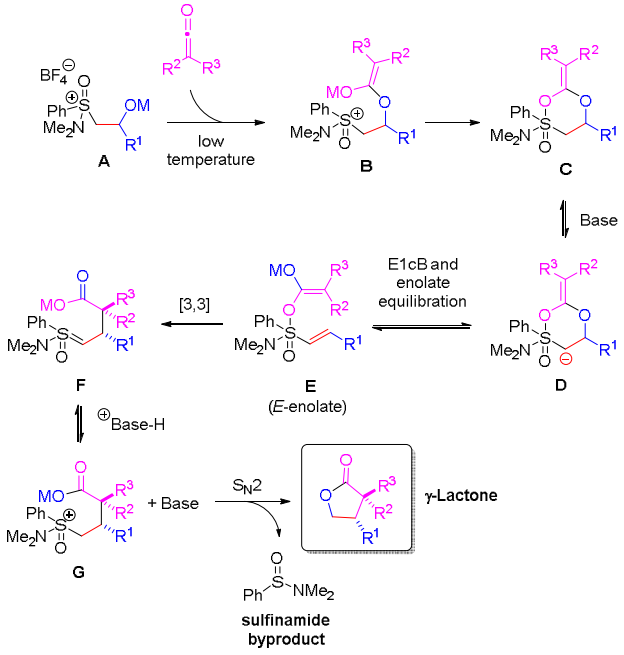
Keywords: disubstituted ketenes; ketoketenes; sulfoxonium ylide; oxosulfonium ylide; γ-lactone; diastereoselective; enantioselective; asymmetric synthesis; aldehydes

The asymmetric synthesis of γ-lactones is a very challenging task, and few successful intermolecular approaches to this problem have been reported.[1] One of the best solutions is the SmI_2-reductive coupling of ephedrinyl acrylates and aldehydes, introduced by Fukuzawa and co-workers in 1997.[2] However, as is usual for chiral auxiliaries, an additional step was necessary in order to attach the auxiliary to the substrate. In recent years we have had success in developing nucleophile-catalyzed reactions of ketenes, and we anticipated that an approach involving ketene chemistry might lead to a versatile entry to γ-lactones, without the need for the use of excess amounts of expensive reagents.[3] In 2013 we showed that aminosulfoxonium ylides could engage aldehydes and ketenes in a sequential one-pot approach to γ-lactones (Scheme 1).[4,5]



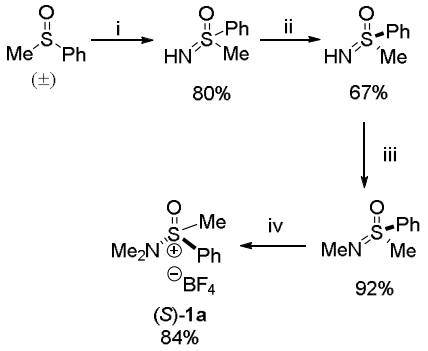
Scheme 1. Diastereoselective synthesis of γ-lactones from reaction of aminosulfoxonium ylide, aldehydes and ketenes.

We proposed that the reaction involved a [3,3]-sigmatropic rearrangement of a sulfurane oxide intermediate, which allowed for high diastereoselectivity to be obtained in the formation of γ-lactones (Scheme 2).[4,6-8] Based on this mechanism, we reasoned that γ-lactones could be formed in enantioselective fashion, provided a suitable enantioenriched aminosulfoxonium salt could be identified. In this letter, we detail our preliminary findings and report that indeed good enantioselectivity in γ-lactone synthesis can be achieved through such a reaction manifold.



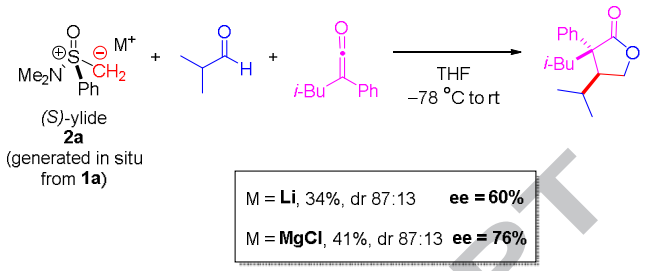
Scheme 2. Proposed mechanism for the formation of γ-lactone.

We began our investigations by evaluating aminosulfoxonium salt **1a**. (*S*)-**1a** was obtained through a 4 step procedure from commerically available methylphenyl sulfoxide, as outlined in Scheme 3.[9,10] Methylphenyl sulfoxide was converted to the sulfoximine derivative by reaction with sodium azide under acidic conditions. After racemic methylphenyl sulfoximine was obtained, it was resolved with (+)-(*S*)-10-camphorsulfonic acid.[10] The enantioenriched methylphenyl sulfoximine was then subjected to methylation using formic acid and formaldehyde (the Eschweiler-Clarke reaction).[9] The final step involved the use of trimethyloxonium fluoroborate to methylate the sulfoximine and access the (dimethylamino)methylphenyl oxosulfonium fluoroborate in enantioenriched form (98% ee).



Scheme 3. (i) NaN_3, H_2SO_4, $CHCl_3$; (ii) (+)-(*S*)-10-camphorsulfonic acid; (iii) formic acid, formaldehyde; (iv) trimethyloxonium fluoroborate.

With the desired enantioenriched sulfoxonium salt in hand, we proceeded to evaluate its effectiveness in reactions with isobutyraldehyde and isobutylphenylketene.[11] These reactants were chosen as we had previously determined that the reaction of racemic aminosulfoxonium ylide, generated from the corresponding tetrafluoroborate salt by treatment with *n*-BuLi, proceeded with very good diastereoselectivity (dr 88:12) and in moderate yield (32%).[4] We then proceeded to evaluate the influence of (*S*)-**1a** on enantioselectivity in γ-lactone formation (Scheme 4). When *n*-BuLi was used as a base, and hence Li as the counterion (M^+), good enantioselectivity (60% ee) and diastereoselectivity was obtained. In addition, when $MgCl_2$ was used as an additive, a slight improvement in enantioselectivity was obtained (76% ee). We speculate that the improvement in this particular case is due to increased chelation (organization) in the transition state. In subsequent substrate scope experiments (Table 2), we evaluated both sets of conditions in order to establish optimal enantioselectivity. In most cases, it was found that best results were obtained with the simple system of M^+ = Li (base = *n*-BuLi), without any need for an additive.



Scheme 4. Optimization of asymmetric reaction.

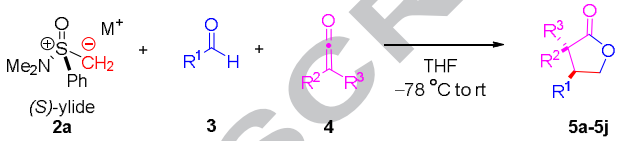


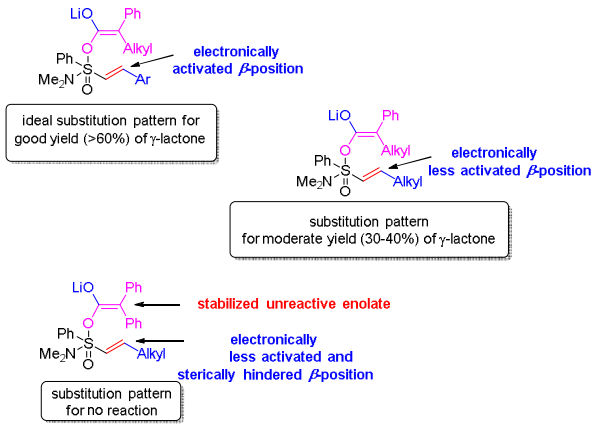
Table 2. Substrate scope of the γ-lactone-forming reaction.[a]

Entry	R^1	R^2	R^3	Yield[b]	dr	ee (%)	Lactone
1[c]	*i*-Pr	*i*-Bu	Ph	41	87:13	76	**5a**
2	2-NO_2Ph	*i*-Bu	Ph	65	92:8	6	**5b**
3	2-MePh	*i*-Bu	Ph	28	95:5	14	**5c**
4	Ph	*i*-Bu	Ph	51	73:27	10	**5d**
5	*i*-Pr	Et	Ph	31	80:20	65	**5e**
6[d]	*i*-Pr	Et	Ph	25	77:23	66	**5e**
7	*i*-Pr	Me	Ph	28	87:13	79	**5f**
8	2-NO_2Ph	Me	Ph	62	90:10	3	**5g**
9	4-NO_2Ph	Ph	Ph	50		34	**5h**
10	*i*-Pr	Ph	Ph	0			
11	2-NO_2Ph	Me	Me	31		21	**5i**
12	4-NO_2Ph	Me	Me	48		7	**5j**

[a] Ylide **2a** generated from **1a** by treatment with *n*-BuLi in all cases. [b] Yields are isolated yields. [c] $MgCl_2$ used as an additive. [d] CuI used as an additive.

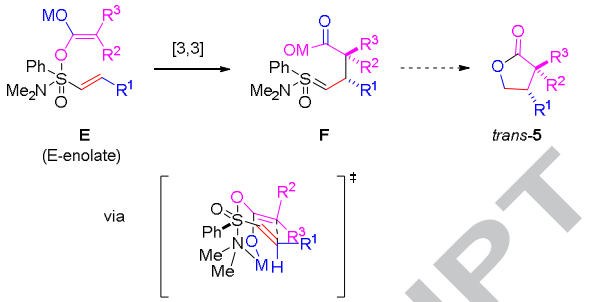
In general, best yields of γ-lactone were obtained with aromatic aldehydes (up to 65%), as had been previously noted in our communication on the racemic variant of this reaction.[4] This is presumably due to the more reactive intermediate **E** that is formed when an aromatic substituent is present at the β-position of the α,β-unsaturated sulfurane oxide intermediate **E**, leading to a preference for [3,3]-sigmatropic rearrangement rather than competing intermolecular side reactions (e.g. aldol reactions). When an aliphatic aldehyde is utilized, the lower reactivity of intermediate **E**, with an aliphatic substituent present at the β-position of the α,β-unsaturated sulfurane oxide intermediate **E**, slows [3,3]-sigmatropic rearrangement, leading to an increase in competing intermolecular side reactions, such as aldol reactions. Not surprisingly, moderate yields (up to 41%) were obtained with aliphatic aldehydes (entry 1, and entries 5-7). A limitation of the methodology was found

when diphenylketene was tested in a reaction with isobutyraldehyde (Entry 10). In that case, no γ-lactone product was formed. This is most likely due to the enolate in **E** being too stabilized, in combination with the α,β-unsaturated sulfurane oxide of **E** lacking sufficient electrophilicity at the β-position (see Scheme 5).



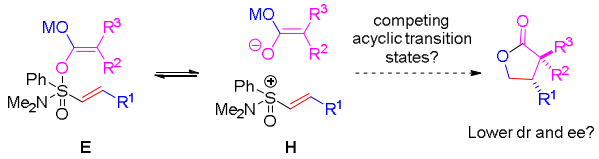
Scheme 5. Intermediate **E** substitution pattern trends for formation of γ-lactone **5**.

Diastereoselectivity in γ-lactone reaction may be rationalized by a [3,3]-sigmatropic rearrangement of sulfurane oxide **E**, involving a six-membered chair-like transition state, where the larger (higher priority) substituents (R^1 and R^3) preferentially occupy pseudoequatorial positions (Scheme 6).[7] We propose that the O-enolate and $-NMe_2$ substituents occupy apical positions at sulfur (in a trigonal bipyramidal geometry), which is consistent with the reported arrangement of cyclic sulfurane oxides bearing electronegative substituents.[8,12] Best levels of diastereoselectivity were observed when a sterically bulky 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 **E** (e.g. entry 2 vs entry 4). [3,3]-sigmatropic rearrangement of intermediate **E**, where the enolate is mainly in the *E*-isomeric form, would provide the *trans*-diastereomer (*anti*-diastereomer) of the γ-lactone. The identity of the major diastereomer (for the analogous racemic series) had previously been confirmed to be the *trans*-isomer by X-ray crystal structure analysis.[4] We define the *trans*-diastereomer of the γ-lactone as the isomer with the highest priority groups at each stereogenic center on opposite sides of the the γ-lactone ring.



Scheme 6. Proposed transition state for [3,3]-rearrangement of intermediate **E**.

Optimal transfer of chirality was observed for those reactions involving an α-branched aliphatic aldehyde (isobutyraldehyde), where enantiomeric excesses of 65-79% ee were observed. Configurationally stable sulfurane oxides are known, and so we speculate that high enantioselectivity may be achieved through the rigid transition state depicted in Scheme 6, where the phenyl substitutent blocks approach by the enolate moiety to the *re* face of the α,β-unsaturated sulfurane oxide.[13] Chelation of the enolate O-atom and the N of the -NMe_2 group by the metal (M = Li or MgCl) may also provide important transition state organization for the achievement of high enantioselectivity and diastereoselectivity. The more reactive aromatic aldehydes (e.g., 4-NO_2PhCHO) gave significantly lower enantioselectivity (3-34% ee). These lower levels of enantioselectivity may be interpreted in terms of a more reactive intermediate (**E**), with an earlier less organized/less defined transition state (lower energy barrier to rearrangement), and correspondingly lower discrimination between competing diastereomeric transition states. Alternatively, intermediate **E** may be in equilibrium with enediolate and α,β-unsaturated sulfurane oxide **H**, leading to lower enantioselectivity via competing acyclic transition states (Scheme 7). Berry pseudorotation of pentacoordinate sulfurane oxide intermediates (particularly of **E**) might also be a factor in the low enantioselectivity observed in some cases.[14] Indeed, lactone **5h** (34% ee) was accompanied by sulfinamide byproduct as a racemate.



Scheme 7. Possible mechanism for erosion of enantioselectivity.

In summary, we have developed a novel route to enantioenriched γ-lactones that is efficient (sequential one-pot reaction of three components), operationally simple, and economically attractive.[15,16] While enantioselectivity is modest in many cases, the highest enantiomeric excess of 79% represents a promising lead

for future investigations using other, as yet untested, chiral non-racemic sulfoxonium salts. Future studies will also focus on the development of catalytic asymmetric variants of the methodology described herein.

Acknowledgments

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15 Experimental procedure for preparation of (−)-**5a**: (*S*)-(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 solution was stirred for 45 min. $MgCl_2$ (0.50 mmol) was then added to the reaction solution under a positive pressure of nitrogen. Transmetallation was assumed complete after 15 min. Isobutyraldehyde (0.25 mmol) was added dropwise and the reaction was stirred for another 1.5 h at −78 °C. Finally, isobutylphenylketene solution (0.25 mmol in 0.5 mL THF) was added to the reaction via syringe pump 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 *ca.* 20 h. The reaction was quenched with water (10 mL) and extracted with ether (3 × 10 mL). The combined organics were dried with $MgSO_4$ and filtered. The crude product was purified by passing through a plug of neutral silica, eluting with a 2% EtOAc:hexane solvent system. The solvent was removed under reduced pressure to afford (−)-**5a** as a colorless oil (26 mg, 41%), with a dr of 87:13 as determined by GC-MS analysis (and confirmed by ^{1}H NMR analysis) of the crude product.

16 Characterization data for (–)-**5a**: HPLC analysis: 76% ee [Daicel Chiralpak AS-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 20.6 min (major), 17.9 min (minor)]; $[\alpha]_D^{23} = -15.7$ (c = 0.15, CH_2Cl_2); IR (thin film): 1766 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$, TMS) for the major diastereomer: δ 7.38-7.31 (m, 5H), 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 180.3, 140.3, 128.7, 127.6, 127.4, 67.5, 53.9, 53.5, 38.7, 26.6, 24.6, 24.4, 24.4, 22.0, 19.0; MS (EI 70eV): 260, 204, 161, 117, 91 m/z; $(M + H)^+$ HRMS m/z calcd for $C_{17}H_{25}O_2^+$: 261.1855; found: 261.1854.

Supplementary Material

Electronic Supplementary Information available: Characterization data and procedures for the preparation of γ-lactones **5a**-**5j**, NMR spectra for **5a** and **5f**.