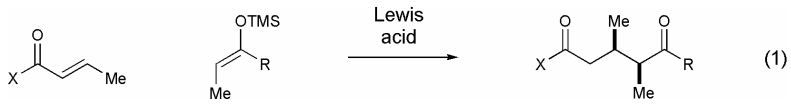
Chapter 3

Development of a General Enantioselective Organocatalytic Mukaiyama-Michael Reaction: Development of a Second-Generation Organocatalyst

I. Introduction

The Mukaiyama-Michael Reaction

The first report of the conjugate addition of silyl enol ethers to α,β-unsaturated carbonyl compounds was made by Mukaiyama in 1974.[1] Since that first report, the conjugate addition of latent enolate equivalents to α,β-unsaturated carbonyl compounds has been termed the Mukaiyama-Michael reaction (equation 1). This reaction is an effective method for the establishment of stereochemical relationships in an acyclic framework.[2] The conjugate addition of latent enolate equivalents to α,β-unsaturated carbonyl compounds is possible under milder conditions and with superior regioselectivity (1,2- vs. 1,4-addition) than metalloenolate conjugate additions.[3-8] There have been many examples of diastereoselective Mukaiyama-Michael reactions, particularly those employing chiral Michael acceptors, but catalytic enantioselective reactions present a greater synthetic challenge and are the ultimate goal of asymmetric Mukaiyama-Michael technology.



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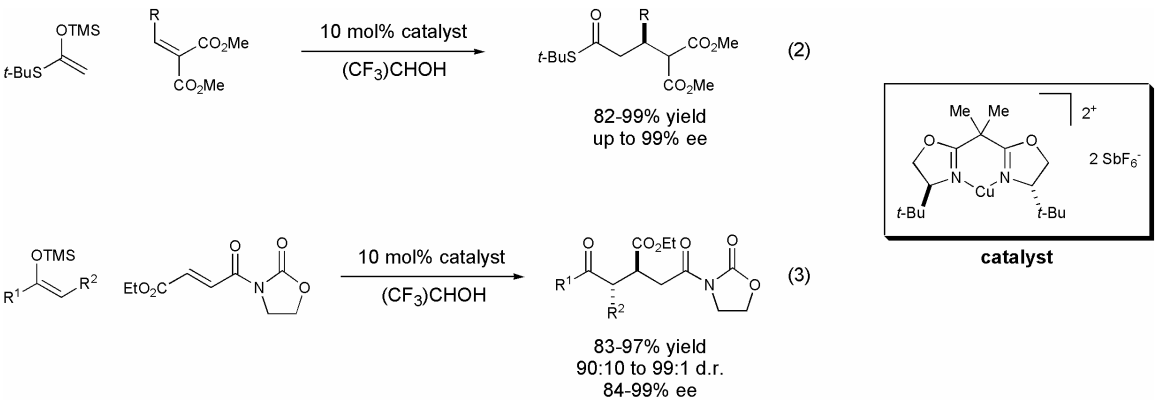
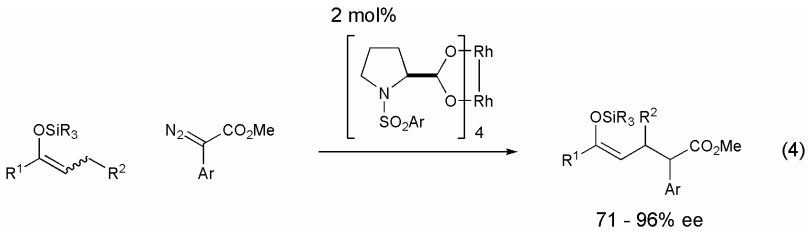
Enantioselective Catalysis of the Mukaiyama-Michael Reaction

There have been many reports of chiral Lewis acid promoted and catalyzed asymmetric Mukaiyama-Michael reactions.[9-25] The most general chiral Lewis acid catalyzed systems have been developed by the Evans laboratory (Scheme 1).[19,20] Using a copper(II) bis(oxazoline) catalyst, an enantioselective Mukaiyama-Michael reaction has been demonstrated with alkylidene malonates as Michael acceptors, and a formal Mukaiyama-Michael reaction has been demonstrated with unsaturated acyl oxazolidinones as Michael acceptors (Scheme 1, equations 2 and 3). The formal Mukaiyama-Michael reaction of acyl oxazolidinones has been shown to proceed through a hetero Diels-Alder/hydrolysis pathway rather than the expected conjugate addition manifold.

Scheme 1. Copper-bis(oxazoline)-catalyzed Mukaiyama-Michael reactions.

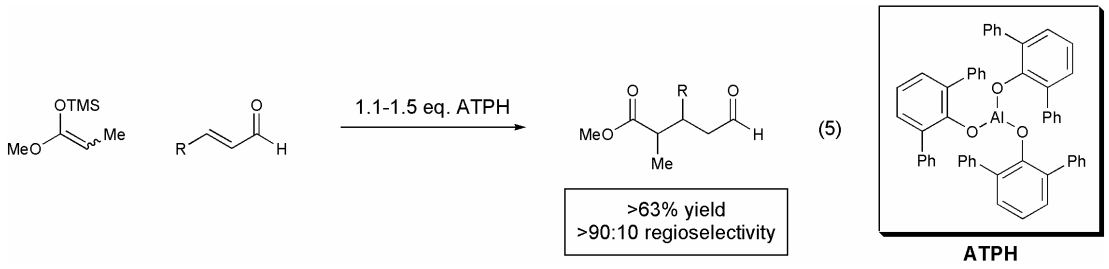


There have been other approaches to the development of an asymmetric Mukaiyama-Michael reaction. The Davies group has reported a formal asymmetric Mukaiyama-Michael reaction that proceeds through the catalytic C-H activation of silyl enol ethers with enantioselectivities as high as 96% (equation 4).[26]



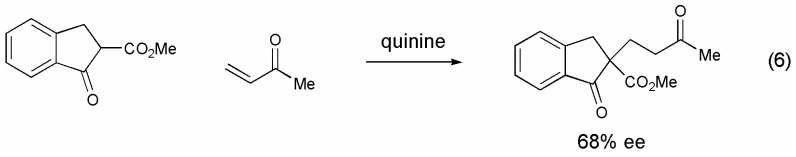
Mukaiyama-Michael Reactions with α,β-Unsaturated Aldehydes

When a Mukaiyama-Michael reaction is attempted between an α,β-unsaturated aldehyde and a latent enolate equivalent, 1,2-addition of the nucleophile to the aldehyde occurs, resulting in a Mukaiyama-aldol reaction. [5-8,27-29] The only example of a Lewis acid catalyzed Mukaiyama-Michael reaction involving α,β-unsaturated aldehydes as Michael-acceptors was reported by the Yamamoto group.[30] An aluminum Lewis acid was developed that completely shields the carbonyl carbon of an α,β-unsaturated aldehyde from nucleophilic attack by a variety of nucleophiles, including silyl ketene acetals (equation 5).

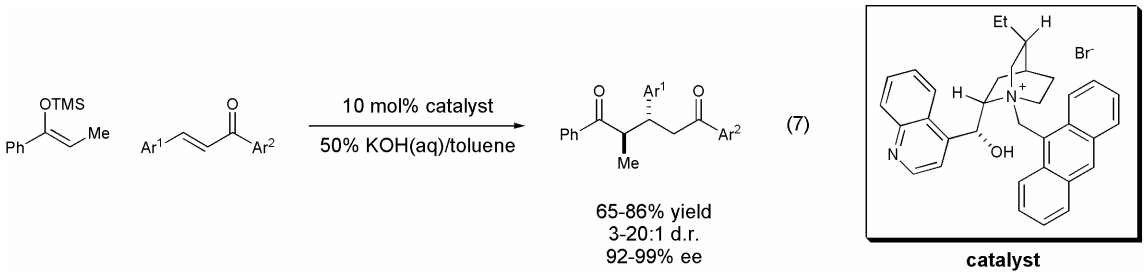


Organocatalysis of the Michael Reaction

The first organocatalytic enantioselective Michael reaction was reported in 1975 (equation 6).[31] Since the initial report, a variety of cinchona alkaloids have been used as catalysts for the Michael addition reaction.[32]



Phase-transfer agents have been used to catalyze the Mukaiyama-Michael reaction.[33,34] The Corey laboratory has demonstrated that chiral quaternary ammonium salts derived from cinchona alkaloids can catalyze the addition of silyl enol ethers to chalcones with excellent selectivity (equation 7).

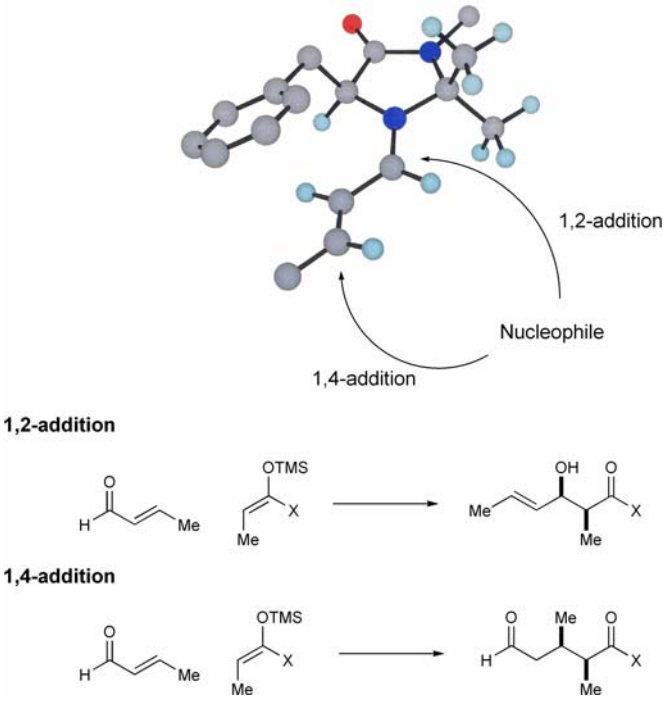


Imidazolidinone-Catalyzed Conjugate Addition

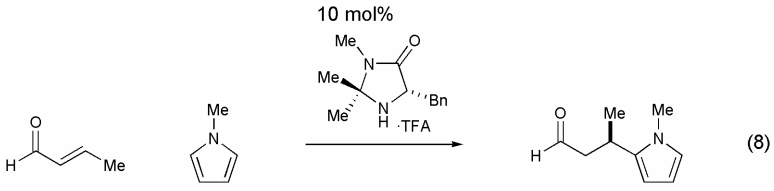
The chemoselectivity of the addition of a silyl ketene acetal to an α,β-unsaturated aldehyde was one of the known challenges to developing an organocatalytic Mukaiyama-Michael reaction. If the proposed reaction was to be successful, the imidazolidinone catalyst developed in the context of the Diels-Alder cycloaddition would need to provide

enough shielding of the iminium carbon to prevent 1,2-addition of silyl ketene acetals to the catalyst-aldehyde adduct (Scheme 2).

Scheme 2. 1,2- versus 1,4-addition to the imidazolidinone-aldehyde adduct.



Previous research in the MacMillan laboratory had shown that the imidazolidinone catalyst is effective at promoting 1,4- over 1,2-additon of pyrroles to α,β-unsaturated aldehydes (equation 8).[35] Therefore, it was believed that the success of the organocatalytic Mukaiyama-Michael was probable.



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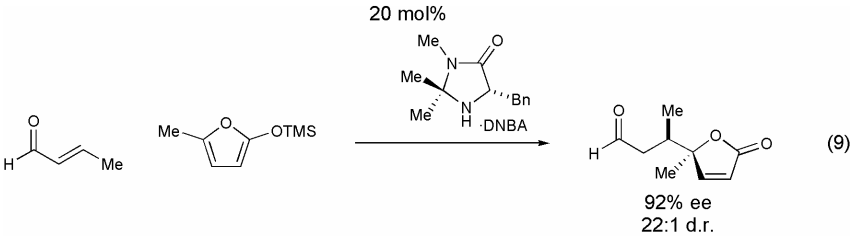
During the course of this research, organocatalysis of the Mukaiyama-Michael reaction was achieved within the context of butenolide synthesis.[36] The conjugate addition of siloxy furans to α,β-unsaturated aldehydes was demonstrated with enantioselectivities up to 98% (equation 9).



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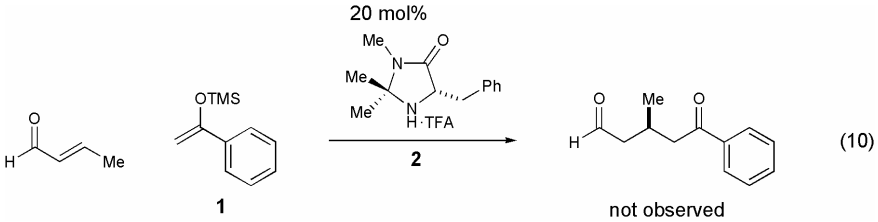
II. Results and Discussion

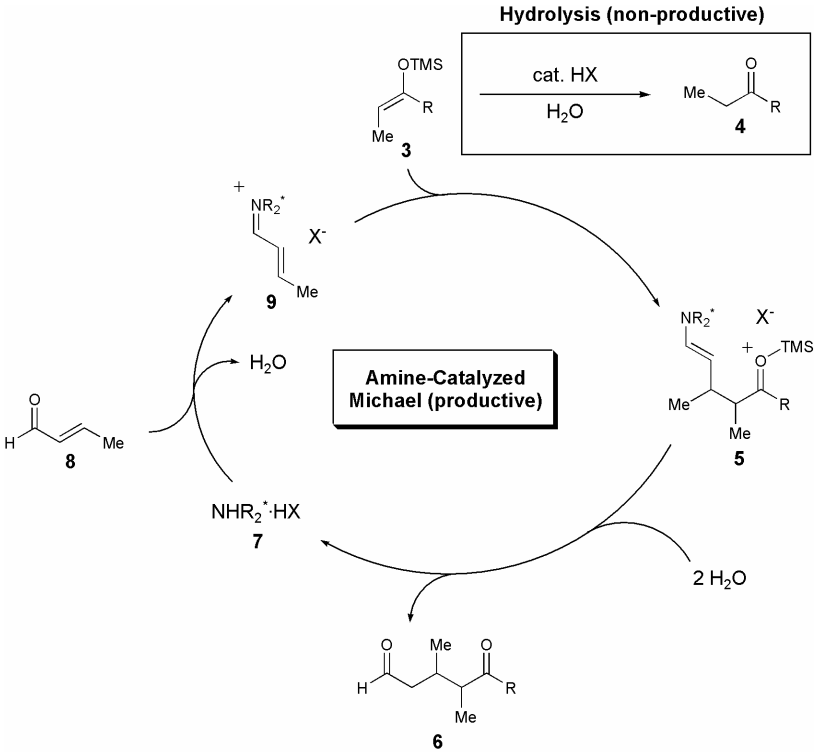
Initial Investigations

The first attempt at developing an organocatalytic Mukaiyama-Michael reaction in the MacMillan laboratory was unsuccessful (equation 10).[37] The only chemical species observed in this reaction were unmodified α,β-unsaturated aldehyde and the ketone derived from hydrolysis of **1**.



Under organocatalytic reaction conditions, two pathways are possible for the nucleophilic silyl enol ether **3** (Scheme 3). The acid catalyzed hydrolysis of silyl enol ether **3** can occur, consuming the reagent and leading to the non-productive formation of the carbonyl compound **4**. Or the silyl enol ether **3** can productively react with the iminium ion **9** formed from the organocatalyst **7** and α,β-unsaturated aldehyde **8**, leading to product adduct **6** regenerating the organocatalyst **7** after hydrolysis.

Scheme 3. Proposed organocatalytic Mukaiyama-Michael catalytic cycle.

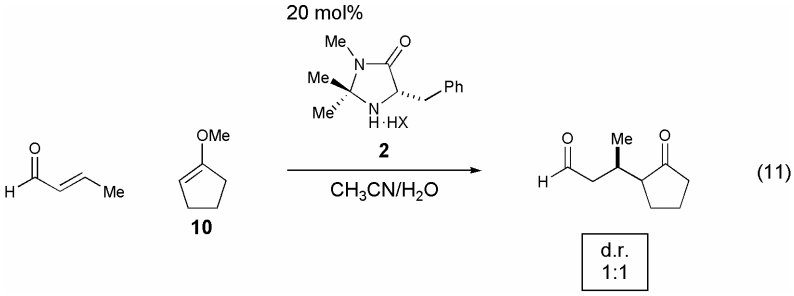


Investigations with Alkyl Enol Ethers

Subsequent study of the organocatalytic Mukaiyama-Michael reaction took this into account. A nucleophile that would be robust enough to survive the acidic, aqueous conditions needed for organocatalysis must be used. Non-aromatic alkyl enol ethers were chosen for study.

Initial studies of the organocatalytic Mukaiyama-Michael reaction examined the conjugate addition of the methyl enol ether **10** with crotonaldehyde. The hydrolysis of the nucleophile **10** plays a significant role in achieving reasonable chemical yields, therefore the effect of the acid co-catalyst was examined.

Table 1. Effect of acid co-catalyst on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the methyl enol ether of cyclopentanone (**10**).[a]

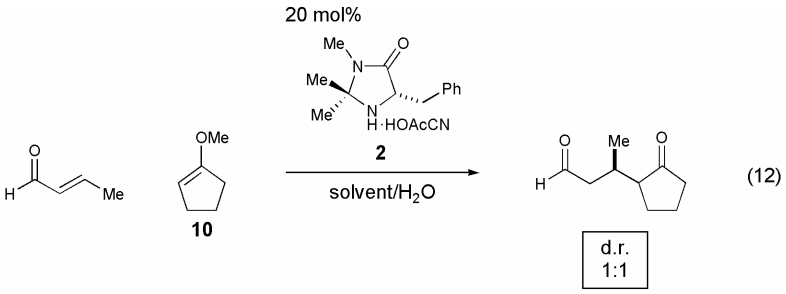


Entry	HX	pK_a (H_2O)	% Conversion[b]	% ee[b]
1	HOAcCN	2.47	55	50
2	DCA	1.35	49	49
3	TFA	0.52	18	49
4	TCA	0.51	14	50
5	PTSA	-1.34	2	--
6	MsOH	-2.6	15	49
7	H_2SO_4	-3.0	7	49
8	HCl	-6.1	10	48
9	HNO_3	-8	8	49
10	$HClO_4$	-10	4	--
11	TfOH	-14	2	--

[a] All reactions performed at -20 °C; [b] Conversion, diastereoselectivity, and enantioselectivity determined by GLC analysis.

The acidity of the Brønsted acid co-catalyst plays a significant role in the reactivity of the silyl ketene acetal nucleophile (Table 1). Only the most weakly acidic co-catalysts examined produced product in moderate yields (49-55%, Table 1, entries 1, 2). All other acid co-catalysts examined proved to be too acidic, hydrolyzing the alkyl enol ether nucleophile **10** rather than catalyzing conjugate addition. Interestingly, the selectivity of the transformation does not appear to be dependent upon the co-catalyst pK_a. All reaction conditions examined resulted in the same diastereoselectivity (1:1), and very similar enantioselectivities (48-50% ee).

Table 2. Effect of solvent on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the methyl enol ether of cyclopentanone (**10**).[a]



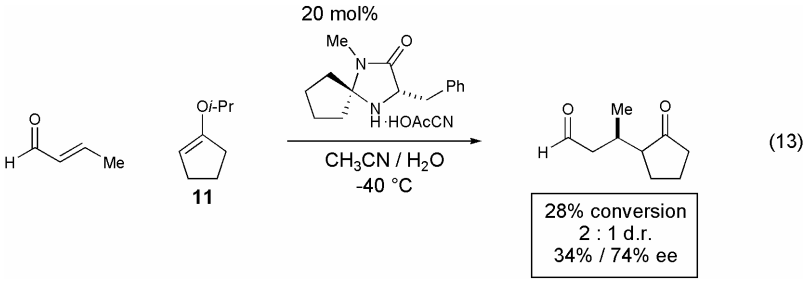
Entry	Solvent	E_T^N	% Conversion[b]	% ee[b]
1	MeOH	0.762	<5	--
2	EtOH	0.654	<5	--
3	*n*-BuOH	0.602	<5	--
4	*i*-PrOH	0.546	8	45
5	CH_3NO_2	0.481	26	49
6	CH_3CN	0.460	33	53
7	DMSO	0.444	<5	--
8	DMF	0.404	<5	--
9	acetone	0.355	9	51
10	CH_2Cl_2	0.309	8	33
11	$CHCl_3$	0.259	5	5
12	DME	0.231	<5	--
13	EtOAc	0.228	<5	--
14	THF	0.207	<5	--
15	1,4-dioxane	0.164	5	39
16	ether	0.117	<5	--
17	toluene	0.099	<5	--
18	hexanes	0.009	<5	--

[a] All reactions performed at -30 °C; [b] Conversion, diastereoselectivity, and enantioselectivity determined by GLC analysis on a Bodman Chiraldex Γ-TA column

A survey of solvents demonstrated that polar aprotic solvents afforded the highest conversions for the conjugate addition of alkyl enol ether **10** to crotonaldehyde (Table 2). Polar protic solvents produced almost no product, instead hydrolyzing the alkyl enol ether (Table 2, entries 1-4). Less polar solvents, while not rapidly hydrolyzing the acid sensitive nucleophile **10**, did not allow sufficient formation of reactive iminium ion intermediate. The lack of significant quantities of iminium ion allowed the relatively

slow alkyl enol ether hydrolysis to dominate under these reaction conditions. Because of its superior performance, yielding product in 53% ee, further studies with alkyl enol ether **10** were performed in acetonitrile (Table 2, entry 6).

Variation in the alkyl group of the alkyl enol ether was examined, and it was quickly determined that those alkyl enol ethers possessing the largest alkyl substituent performed the best under organocatalytic conditions. Imidazolidinone architectures surveyed in the development of the organocatalytic Diels-Alder reaction (Chapter 2, Tables 6 and 7) were studied as catalysts for the organocatalytic Mukaiyama-Michael reaction. Through these studies and others, reaction conditions were optimized to yield product from alkyl enol ether **11** and crotonaldehyde with good enantioselectivity for the minor diastereomer (equation 13, 2:1 d.r., 74% ee, minor diastereomer).



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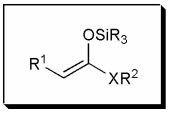
Investigations with Silyl Ketene Acetals

In an effort to increase the yield and selectivity of the organocatalytic Mukaiyama-Michael reaction, a different class of nucleophile was examined. Silyl ketene acetals were chosen because they are common nucleophiles for Mukaiyama-Michael reactions, and they allow access to a large variety of architectures (Figure 1).[5]

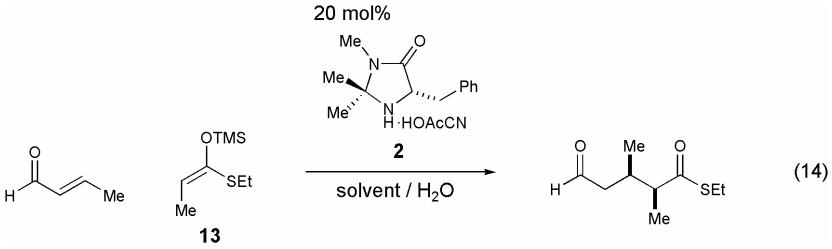
Figure 1. Silyl ketene acetals are potential nucleophiles for the organocatalytic Mukaiyama-Michael reaction.



SiR_3 = TMS, TES, TBS, TPS, TBDPS, TIPS
R^1 = H, alkyl, aryl, OR
X = O, S
R^2 = Me, Et, Ph, *i*-Pr, *t*-Bu

Silyl ketene acetals derived from thioesters were first examined. Initial studies were performed with the trimethylsilyl ketene acetal derived from *S*-ethyl thiopropionate (**13**) and crotonaldehyde. It was quickly discovered that Mukaiyama-Michael reactions with this class of substrates do not occur at temperatures above -30 °C. All subsequent studies were performed at cryogenic temperatures.

Table 3. Effect of solvent on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and the silyl ketene acetal **13**.[a]



Entry	Solvent	E_t^N	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	*i*-PrOH	0.546	86	1:1.3	17
2	CH_3NO_2	0.481	81	3.3:1	60
3	CH_3CN	0.460	79	1.6:1	54
4	DMSO	0.444	23	1:1.8	21
5	DMF	0.404	36	1:1.9	19
6	acetone	0.355	80	2.1:1	56
7	CH_2Cl_2	0.309	85	3.5:1	62
8	$CHCl_3$	0.259	58	1.3:1	61
9	DME	0.231	67	1:1.2	23
10	EtOAc	0.228	81	3.0:1	53
11	THF	0.207	64	3.4:1	54
12	1,4-dioxane	0.164	69	2.9:1	53
13	ether	0.117	74	4.1:1	55
14	toluene	0.099	59	1.4:1	52
15	hexanes	0.009	64	1.3:1	53

[a] All reactions performed at -50 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The conjugate addition of silyl ketene acetal **13** to crotonaldehyde was examined in a variety of solvents (Table 3). It quickly became apparent that, with few exceptions, the organocatalytic Mukaiyama-Michael reaction between silyl ketene acetal **13** and crotonaldehyde shows little solvent dependence. The combination of the highest conversion and selectivities was observed in methylene chloride, a solvent of intermediate polarity (85% conversion, 3.5:1 *syn:anti*, 62% ee, Table 3, entry 7). Acetone, chloroform, and ether did not perform significantly worse (Table 3, entries 6, 8,

13). Further experimentation revealed that the solvent of choice may vary for different substrate combinations.

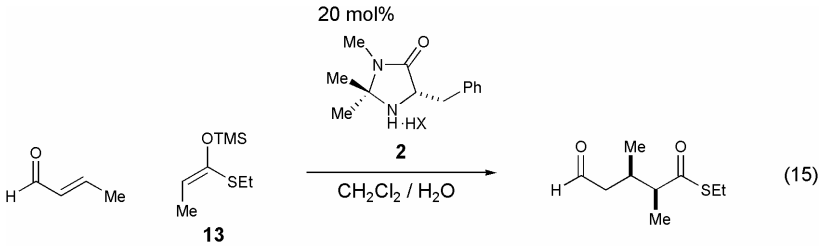
The effect of concentration on the organocatalytic Mukaiyama-Michael was examined. Conversion and selectivity of the conjugate addition increased with concentration up to 2.0 M, relative to the limiting reagent. At concentrations higher than 2.0 M, the conversion and selectivity of the process sharply decreased.

The effect of the co-catalyst acid on the addition of silyl ketene acetal **13** to crotonaldehyde was carefully examined because of the known silyl ketene hydrolysis side reaction and the known acid catalyzed nature of this hydrolysis (Table 4). A strong dependence on co-catalyst pK_a became immediately evident. Weakly acidic co-catalysts with pK_a's greater than 3 (Table 4, entries 1 and 2) did not yield product under reaction conditions. It is believed that the reaction medium is not acidic enough to form sufficient quantities of reactive iminium ion. Therefore, without a competent electrophile (iminium ion), the silyl ketene acetal **13** can only hydrolyze under the reaction conditions. Strongly acidic co-catalysts with pK_a's less than 0 (Table 4, entries 8-15) did not yield product either. These co-catalysts present the opposite problem. While the acid co-catalysts are acidic enough for the formation of significant quantities of reactive iminium ion, the strong acids also significantly promote the hydrolysis of the silyl ketene acetal **13**.

It is only when acid co-catalysts with intermediate acidities are used (Table 4, entries 3-7) that moderate quantities of Mukaiyama-Michael adduct are detected. These catalysts are acidic enough to form sufficient quantities of reactive iminium ion but not acidic enough to significantly promote the hydrolysis of silyl ketene acetal **13**. It was discovered through additional experimentation that the optimal co-catalyst can vary with

different substrate combinations. In general, at lower the reaction temperatures, more acidic co-catalysts were more effective.

Table 4. The effect of co-catalyst pK_a on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13**.[a]



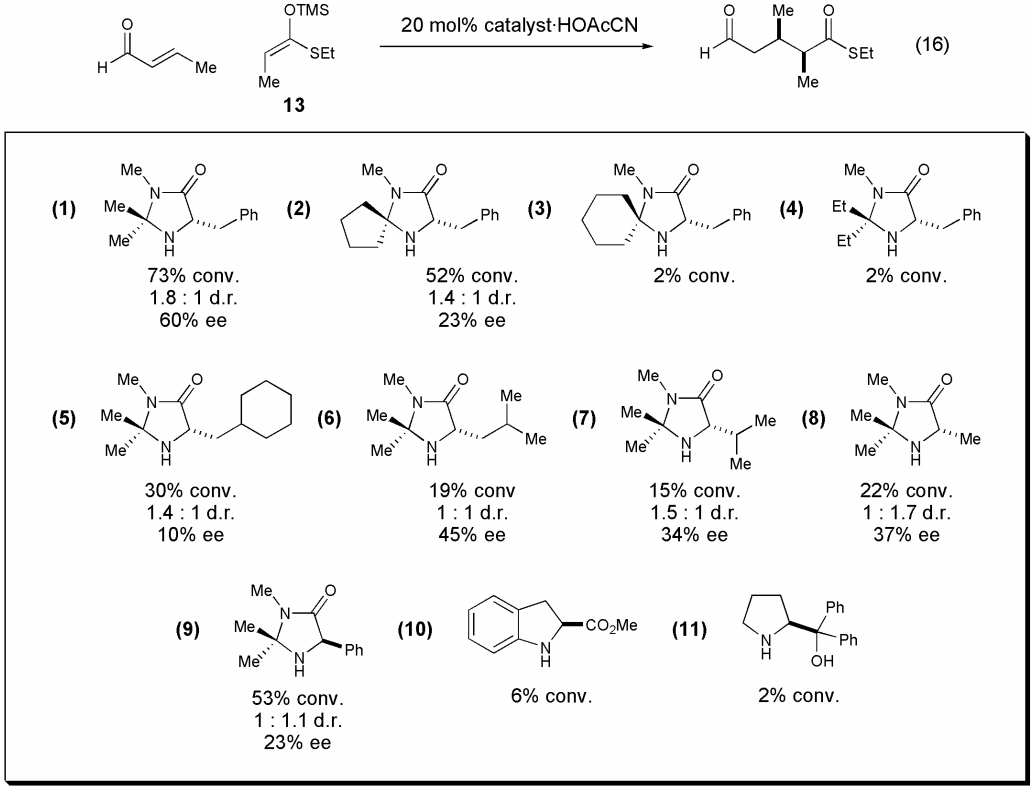
Entry	HX	$pK_a(H_2)$	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	HOAc	4.76	0	--	--
2	HF	3.18	1	--	--
3	HOAcCN	2.47	54	2.6:1	66
4	DBA	1.48	34	2.2:1	72
5	DCA	1.35	31	2.5:1	66
6	DFA	1.34	42	2.5:1	62
7	TCA	0.51	14	2.6:1	66
8	PTSA	- 1.34	3	--	--
9	HNO_3	- 1.44	0	--	--
10	MsOH	- 2.6	3	--	--
11	H_2SO_4	- 3.0	5	--	--
12	HCl	- 6.1	2	--	--
13	HBr	- 9.0	5	--	--
14	$HClO_4$	- 10	0	--	--
15	TfOH	- 14	11	--	--

[a] All reactions performed at -50 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

A variety of chiral secondary amines were surveyed as potential catalysts to assess the reactivity and selectivity of various structural architectures (Table 5). Catalysts that had promoted the organocatalytic Diels-Alder reaction with good yield (Table 5, entry 10) did not catalyze the Mukaiyama-Michael reaction, and catalyst architectures that failed to catalyze the organocatalytic Diels-Alder reaction also failed to

catalyze the Mukaiyama-Michael reaction (Table 5, entry 11). Imidazolidinone catalysts were the only structural framework to yield product in significant quantities. Increasing the steric demand of the imidazolidin-4-one framework proved detrimental to the transformation. As the steric demand of the geminal substituents at the 2-position of the imidazolidin-4-one ring was increased (Table 5, entries 1-4), the conversion of the Mukaiyama-Michael reaction was reduced from 73% to trace amounts. An increase in steric demand at the 5-position of the imidazolidin-4-one ring also produced unfavorable results. When the size of the 5-substituent was increased (Table 5, entries 5-8) the conversion also decreased from 73% to 15-53%.

Table 5. Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13** with representative amine catalysts.[a]



[a] All reactions performed at -50 °C; Conversion determined by GLC analysis; Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; Enantioselectivity reported for major diastereomer.

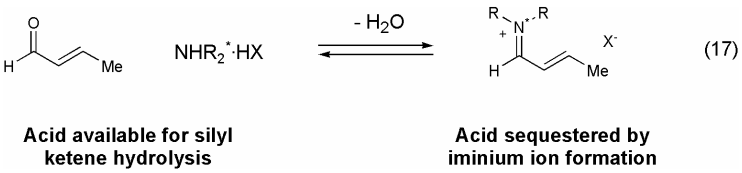
In an attempt to increase the chemical yield of the process, varying ratios of amine and acid co-catalyst were examined. In the end, it was determined that a ratio of unity between the amine and Brønsted acid was most favorable. When fewer equivalents of acid than amine were used, the reaction proceeded more slowly, but approached the same overall yield. That is, both conjugate addition and silyl ketene acetal hydrolysis appeared to be retarded equally. When more equivalents of acid were used than amine, greater hydrolysis of the nucleophile was observed, and chemical yields decreased.

Formation of iminium ion was attempted without Brønsted acid co-catalyst, using the bis-sulfonamide developed by the Crabtree laboratory to promote iminium ion formation between the α,β-unsaturated aldehyde and the free base of imidazolidinone **2** in the absence of protic acid.[38] Unfortunately, iminium ion formation using this hydrogen-bonding catalyst did not occur below -20 °C, and rapid hydrolysis of the silyl ketene acetals occurred above this temperature.

After a through investigation into reaction conditions and catalyst architecture, the most reactive and selective catalyst examined for the Mukaiyama-Michael reaction was benzyl imidazolidinone **2** (73% conversion, 1.8:1 *syn:anti*, 60% ee, *syn* isomer). It became apparent that the imidazolidinone catalyst developed for the organocatalytic Diels-Alder reaction would not effectively catalyze a Mukaiyama-Michael reaction.

Development of a Second-Generation Organocatalyst

A more reactive and selective organocatalyst was needed for the organocatalytic Mukaiyama-Michael reaction. Two design features were necessary to accomplish this goal: (1) an increase in reaction rate and (2) increased enantiofacial discrimination.

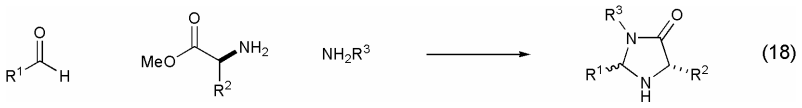


It was hypothesized that increasing the nucleophilicity of the catalyst nitrogen would increase the rate of iminium ion formation and, therefore, increase the reaction rate. By increasing the rate of iminium ion formation, the time the catalyst exists as an acid salt under reaction conditions is also reduced, thereby decreasing the rate of silyl ketene acetal hydrolysis (equation 17). This should effectively favor conjugate addition of the silyl ketene acetal over hydrolysis, increasing the conversion of the transformation (Scheme 3).

To develop a useful organocatalytic Mukaiyama-Michael reaction, the new catalyst must also show an increase in enantioselectivity. This could be accomplished by two different methods. The reactivity of the catalyst could be increased, thereby allowing the organocatalytic Mukaiyama-Michael reaction to be performed at lower temperatures, increasing the observed enantioselectivity, or the steric demand of the portion of the catalyst architecture that shields one π-enantioface of the reactive olefin could be increased. This would increase the enantioselectivity of the process without the need for a decrease in temperature. Ideally, the new organocatalyst should both show increased reaction rates and an increase in enantioselectivity relative to the first-generation imidazolidinone **2**.

The modular nature of the imidazolidinone catalyst lent itself well to these investigations (equation 18). It was believed that modification at the 2-position of the

imidazolidin-4-one catalyst would realize the design goals for the new organocatalyst.[39] Synthesizing an imidazolidinone catalyst using an aldehyde rather than a ketone removes steric congestion from the fully substituted 2-position of the imidazolidinone by introducing a hydrogen atom at that position. This decrease in steric congestion on the imidazolidinone ring should increase the nucleophilicity of the catalyst, fulfilling the first design goal. Prudent choice of the aldehyde could also increase the coverage of the blocked enantioface, meeting the requirements of the second design goal.

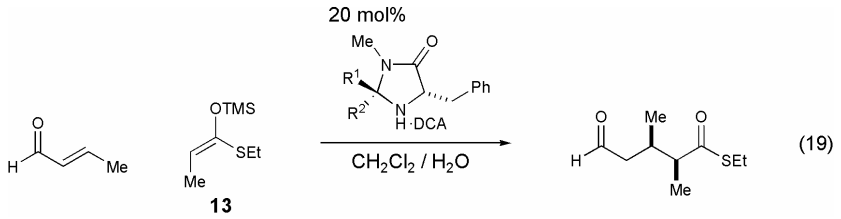


(18)

To this end, several different imidazolidinone catalysts were synthesized with differing substitution at the 2-position of the imidazolidin-4-one catalyst, and the Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13** was used to evaluate the new catalysts (Table 6). All catalysts synthesized with a *cis* relationship between the 2- and 5-substituents showed higher selectivities and conversions than the original *gem*-dimethyl imidazolidinone catalyst **2** (Table 6, entries 1, 3, 5, 7). Those catalysts synthesized with a *trans* relationship showed either no significant change in reactivity or a decrease in reactivity relative to imidazolidinone catalyst **2** (Table 6, entries 1, 2, 4, 6). The best performing catalyst examined, imidazolidinone catalyst **19** ((2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one) increased conversion from 40% to 53% and, more significantly, increased enantioselectivity from 58% to 83% ee (Table 6, entries 1 and 7). In addition, the reaction catalyzed by imidazolidinone **19** showed complete consumption of silyl ketene

acetal **13** in 12 h, a considerably faster reaction time than was previously observed under similar reaction conditions using catalyst **2** (24 h).

Table 6. Effect of imidazolidinone structure on the Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **13**.[a]



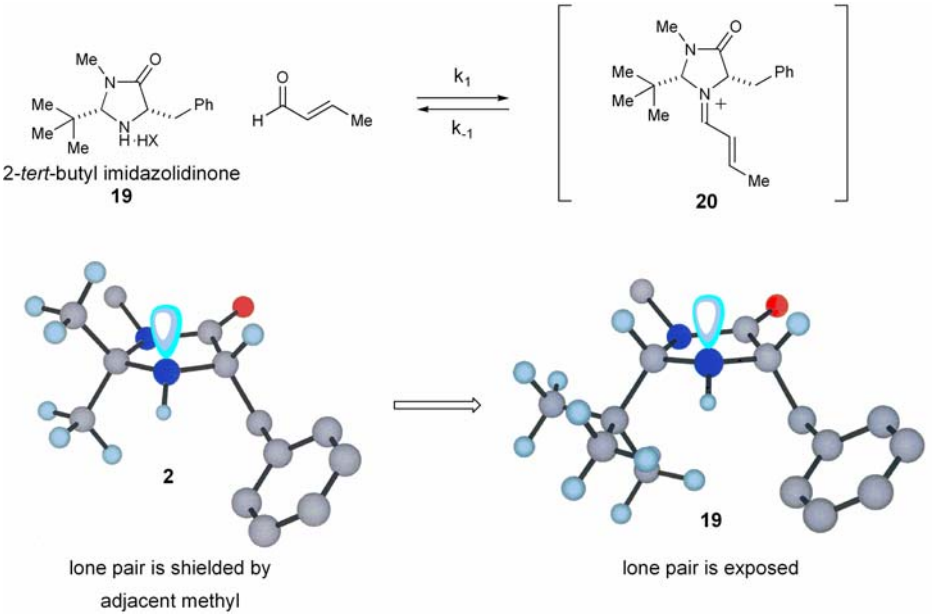
Entry	Catalyst	R^1	R^2	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	**2**	Me	Me	40	1.2:1	58
2	**14**	*i*-Pr	H	47	2.7:1	42
3	**15**	H	*i*-Pr	54	2.4:1	68
4	**16**	Ph	H	36	1.5:1	47
5	**17**	H	Ph	52	1:1.4	61
6	**18**	*t*-Bu	H	17	2.4:1	61
7	**19**	H	*t*-Bu	53	2.3:1	83

[a] All reactions performed at -40 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The *cis*-relationship between the *tert*-butyl and benzyl substitutents on imidazolidinone catalyst **19** allows the increase in reactivity over catalyst **2**. Computational studies of the two catalysts show the decrease in steric congestion around the nucleophilic nitrogen on the new catalyst **19** (Figure 2).[40] The first catalyst developed (**2**) has an eclipsing interaction between the nucleophilic nitrogen lone pair and a methyl group at the 2-position. This reduces the overall nucleophilicity of the nitrogen atom and impedes the reaction rate. By removing the methyl group and replacing it with hydrogen, as in catalyst **19**, the nitrogen lone pair is unencumbered on one side of the imidazolidinone ring and, therefore, is more nucleophilic. This increases the rate of iminium ion formation, increasing the overall rate of the Mukaiyama-Michael reaction.

This also decreases the amount of free acid present in the reaction medium, reducing hydrolysis of the silyl ketene acetal, and increasing conversion.

Figure 2. The second-generation imidazolidinone catalyst **19** increases reaction rates.

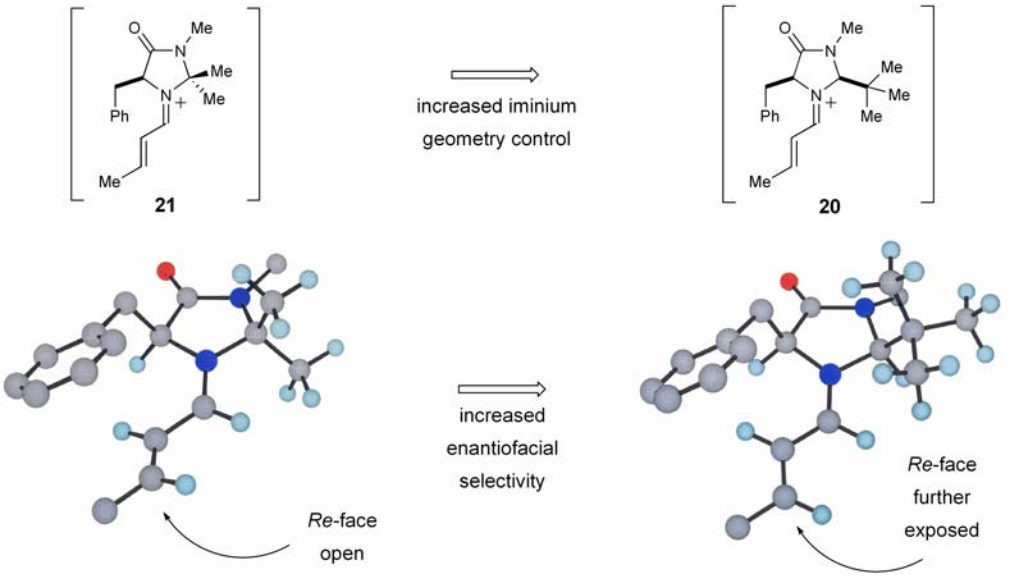


The increase in enantioselectivity is also apparent from the computational study (Figure 3).[40] The steric bulk of the 2-*tert*-butyl group effectively controls the iminium ion geometry. The calculated energy difference between the two iminium ions possible from condensation of catalyst **19** with an α,β-unsaturated aldehyde is 9 kJ·mol^{-1}, favoring the (*Z*)-iminium ion shown. The magnitude of this number supports the conclusion that the Mukaiyama-Michael reaction occurs primarily through only one iminium ion geometry.

Additionally, the large *tert*-butyl substituent provides greater coverage of the blocked π-enantioface relative to the first generation imidazolidinone catalyst adduct **21** (Figure 3). The exposed π-enantioface of the second-generation catalyst adduct **20** is also

more accessible relative to the first generation catalyst adduct **21** due to the lack of a methyl substituent on the exposed face of the imidazolidinone ring. The strong control of iminium ion geometry and the increased coverage one π-enantioface of the catalyst substrate adduct **20** both serve to increase the enantioselectivity of the Mukaiyama-Michael conjugate addition, meeting the second catalyst design goal.

Figure 3. The second-generation imidazolidinone catalyst **19** increases enantioselectivity.

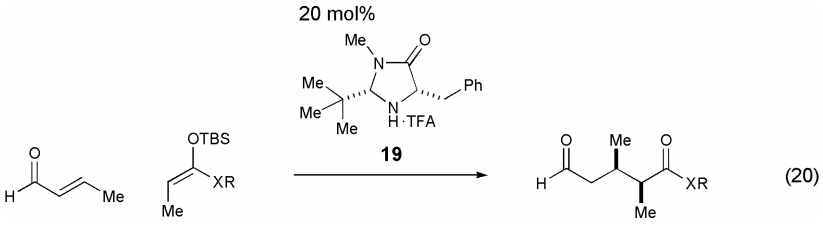


Investigations with the Second-Generation Organocatalyst

With the second generation imidazolidinone catalyst **19** identified, the nature of the silyl group on the silyl ketene acetal nucleophile was then examined. Silyl ketene acetals were generated from *S*-ethyl propionate with a variety of silyl groups. It became evident that *tert*-butyldimethylsilyl ketene acetals were the substrate of choice for the organocatalytic Mukaiyama-Michael reaction. Silyl groups of less steric bulk and less stability towards acid (trimethylsilyl, triethylsilyl, and triphenylsilyl) yielded products in

lower conversion and selectivity.[41] Silyl ketene acetals synthesized with triisopropylsilyl groups, a silyl group showing greater stability towards acid than *tert*-butyldimethylsilyl, proved too stable and did not yield product in higher selectivities than *tert*-butyldimethylsilyl ketene acetals.

Table 7. Effect of silyl ketene acetal alkyl group variation on the Mukaiyama-Michael reaction of crotonaldehyde and representative silyl ketene acetals.[a]



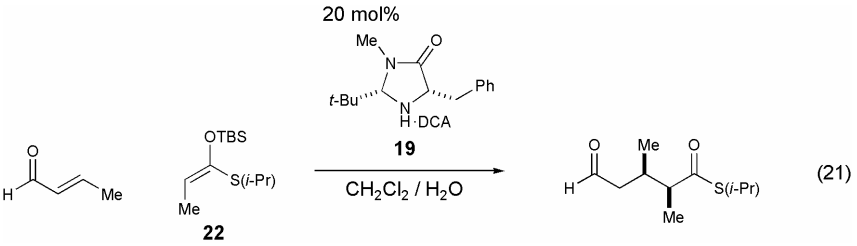
Entry	XR	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	O(*t*-Bu)	0	--	--
2	SPh	0	--	--
3	SMe	38	3.2:1	91
4	SEt	43	2.6:1	86
5	S(*i*-Pr)	70	5.8:1	90
6	S(*t*-Bu)	38	5.4:1	86
7	1-pyrrole	90	1:8	78

[a] All reactions performed in CH_2Cl_2 at -78 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

The effect of varying the alkyl component of the silyl ketene acetal was examined (Table 7). It was expected that an increase in the steric demand of this portion of the nucleophile's architecture would increase the selectivity of the transformation. This was true, but to a defined limit. Ester-derived silyl ketene acetals (Table 7, entry 1) and *S*-phenyl silyl ketene acetals (Table 7, entry 2) were easily hydrolyzed under reaction conditions and did not yield product. As the *S*-alkyl substituent increased in size from methyl to isopropyl (Table 7, entries 3-5), the conversion and selectivity of the organocatalytic Mukaiyama-Michael increased to 70% conversion, 5.8:1 d.r., and 90%

ee. Increasing the size of the *S*-alkyl substituent to *tert*-butyl decreased the selectivity and significantly decreased the conversion of the transformation (Table 7, entry 6). Examination of silyl ketene acetals derived from 1-acyl pyrroles yielded conjugate addition products in excellent yields and selectivities (90% yield, 1:8 d.r., 78% ee, Table 7, entry 7), but with a diastereoselectivity opposite that of products synthesized from thioester-derived silyl ketene acetals.

Table 8. Effect of the amount of water on the organocatalytic Mukaiyama-Michael reaction between crotonaldehyde and silyl ketene acetal **22**.[a]



Entry	Eq. H_2O	% Conversion[b]	*syn:anti*[b]	% ee[c,d]
1	0	61	7.3:1	91
2	1	85	5.0:1	90
3	2	85	5.4:1	89
4	4	67	6.8:1	90

[a] All reactions performed at -55 °C; [b] Determined by GLC analysis; [c] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [d] Enantioselectivity reported for major diastereomer.

In the course of the conjugate addition of a silyl ketene acetal to an α,β-unsaturated aldehyde, one equivalent of a protic species must be consumed to protonate the conjugate addition adduct and scavenge the silyl group. Water had been used as the protic species of choice, and the stoichiometry of this reagent was examined (Table 8). The addition of one equivalent of water to the reaction was determined to be the optimum condition for the organocatalytic Mukaiyama-Michael reaction (85% conversion, 5.0:1 *syn:anti*, 90% ee *syn*, Table 8, entry 2). When no water was added to the reaction

mixture, lower conversion to product was observed (61% conversion, Table 8, entry 1). The conversion of the transformation is not adversely affected until four equivalents of water are used (67% conversion, 6.8:1 *syn:anti*, 90% ee *syn*, Table 8, entry 4).

Other protic agents were also examined as silyl scavengers. A variety of alkyl alcohols, fluorinated alcohols and phenols were examined, but no reagent performed better than water. Therefore, one equivalent of water was used as the silyl scavenger in all subsequent organocatalytic Mukaiyama-Michael reactions.

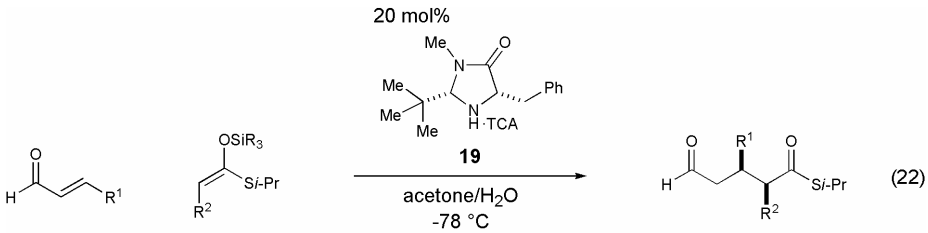
The stoichiometry of the transformation was also examined. It was believed that an excess of aldehyde produced favorable reaction conditions for the conjugate addition of silyl ketene acetals by sequestering most of the catalyst salt as iminium ion. This hypothesis held under experimental examination. Reactions performed with the silyl ketene acetal as the limiting reagent and an excess of α,β-unsaturated aldehyde showed higher conversions and yields than reactions performed with excess silyl ketene acetal and a limiting amount of α,β-unsaturated aldehyde.

Substrate Scope

With an optimized second generation organocatalyst identified and reaction conditions thoroughly examined, the ability of imidazolidinone **19** to catalyze a variety of conjugate additions was examined. All reactions were performed under a wet, aerobic atmosphere, in contrast with Lewis acid catalyzed Mukaiyama-Michael reactions. The organocatalytic reaction also utilizes α,β-unsaturated aldehydes directly as substrates unlike asymmetric Lewis acid catalyzed Mukaiyama-Michael reactions.

The synthesis of *syn*-Mukaiyama-Michael products was first examined (Table 9). The reaction is quite general with respect to the α,β-unsaturated aldehyde structure; variation of the β-substituent of the α,β-unsaturated aldehyde is possible without loss in enantioselectivity (≥4:1 *syn:anti*, 90-91% ee *syn*, Table 9, entries 1-4). The conjugate addition is also tolerant of varying substitution on the nucleophilic silyl ketene acetal, tolerating extended alkyl chains (R^2 = Et, 76% yield, 4:1 *syn:anti*, 94% ee *syn*, Table 9, entry 5) and oxygenation (R^2 = OBn, 82% yield, >20:1 *syn:anti*, 90% ee *syn*, Table 9, entry 6).

Table 9. Organocatalytic synthesis of *syn*-Mukaiyama-Michael products.[a]



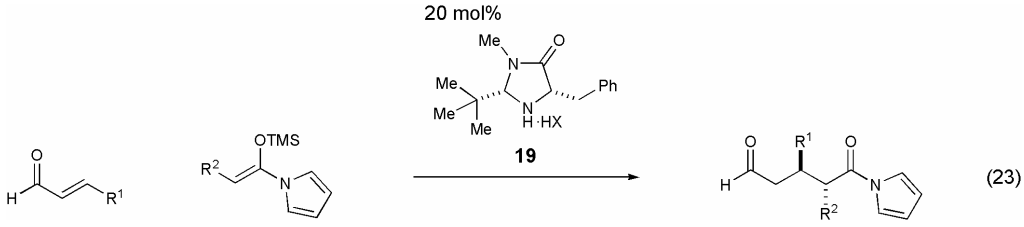
Entry	R^1	R^2	SiR_3	% Yield	*syn:anti*[e]	% ee[f,g]
1	Me	Me	TBS	76	10:1	90
2	*n*-Pr	Me	TBS	62	6:1	90
3[b]	Ph	Me	TMS	50	20:1	90[h]
4	CO_2Me	Me	TMS	73	4:1	91
5[c]	Me	Et	TBS	76	4:1	94
6[d]	Me	OBn	TBS	82	>20:1	90

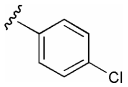
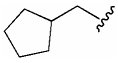
[a] All reactions performed at 2 M with one equivalent of H_2O; [b] Reaction performed with 7% (v/v) cyclohexane; [c] Reaction performed in ether; [d] Reaction performed in methylene chloride with TFA co-catalyst; [e] Determined by ^1H NMR analysis; [f] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [g] Enantioselectivity reported for major diastereomer; [h] Absolute configuration assigned by derivitization and XRD analysis.

Examination of the reaction conditions employed for the various Mukaiyama-Michael reactions with thioester derived silyl ketene acetals reveals that one reaction condition is not appropriate for all substrates examined. This due to the varying reactivity of the aldehydes and silyl ketene acetals examined. α,β-Unsaturated aldehydes

that form more stable iminium ions (R^1 = Ph, Table 9, entry 3) or more reactive iminium ions (R^1 = CO_2Me, Table 9, entry 4) require more reactive silyl ketene acetals to yield reasonable amounts of product (SiR_3 = TMS, Table 9, entries 3, 4). In one case (Table 9, entry 6), a different acid co-catalyst was determined to be optimal, and half of the substrates examined (Table 9, entries 3, 5, 6) proved to require different solvent systems for optimal performance.

Table 10. Organocatalytic synthesis of *anti*-Mukaiyama-Michael products.[a]



Entry[b]	R^1	R^2	HX	% Yield	*syn:anti*[c]	% ee[d,e]
1	Me	Me	TCA	92	1:17	83[f]
2	*n*-Pr	Me	DNBA	56	1:4	93
3		Me	TFA	74	1:3	98
4	Me	OBn	TBA	69	1:>20	93[f]
5	Me		TBA	68	1:10	88
6	Me	Ph	TfOH	78	1:3	87

[a] All reactions performed at 2 M with one equivalent of H_2O; [b] See experimental section for solvent and temperature; [c] Determined by ^{1}H NMR analysis; [d] Enantioselectivity determined by conversion to the corresponding acyl oxazolidinone and subsequent HPLC analysis; [e] Enantioselectivity reported for major diastereomer; [f] Absolute configuration assigned by derivitization to a known compound.

The synthesis of *anti*-Mukaiyama-Michael products was then examined (Table 10). These products can be accessed by simply using a silyl ketene acetal with the opposite olefin geometry; silyl ketene acetals derived from 1-acyl pyrroles were chosen for this purpose. The reaction is quite general with respect to the α,β-unsaturated aldehyde structure; variation of the β-substituent of the α,β-unsaturated aldehyde is

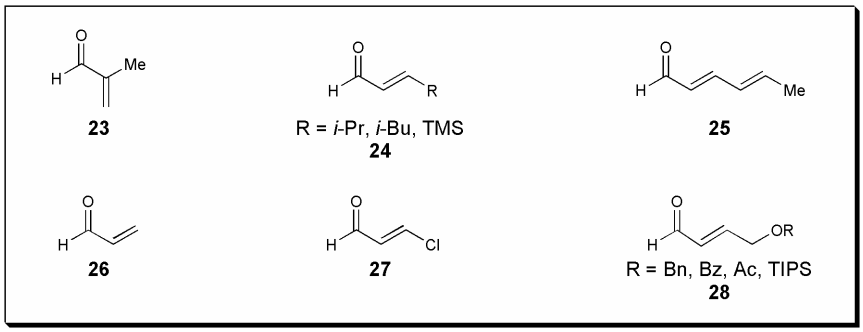
possible while retaining good to excellent enantioselectivity (1:≥3 *syn:anti*, 83-98% ee *anti*, Table 10, entries 1-3). The conjugate addition is also tolerant of varying substitution on the nucleophilic silyl ketene acetal, tolerating oxygenation (R^2 = OBn, 69% yield, 1:>20 *syn:anti*, 93% ee *anti*, Table 10, entry 4), extended alkyl chains (R^2 = CH_2Cp, 68% yield, 1:10 *syn:anti*, 88% ee *anti*, Table 10, entry 5), and aromatic substitution (R^2 = Ph, 78% yield, 1:3 *syn:anti*, 87% ee *anti*, Table 10, entry 6).

As was the case for the Mukaiyama-Michael reactions involving silyl ketene acetals derived from thioesters, the reaction conditions for different substrate combinations varies. Each set of substrates examined has its own optimum solvent or solvent combination, and most reactions use different acid co-catalysts. Acyl pyrrole-derived silyl ketene acetal nucleophiles appear to be much more sensitive to reaction conditions than thioester-derived silyl ketene acetals.

Limitations

While the organocatalytic Mukaiyama-Michael reaction is possible with a variety of structurally diverse substrates, there are certain substrate architectures that are not compatible with these reaction conditions. α,β-Unsaturated aldehydes possessing an α-substituent (**23**) are not competent substrates (Figure 4). It is believed that these substrates do not form significant concentrations of reactive iminium ion. This class of aldehydes has yet to prove competent for any secondary amine-catalyzed LUMO-lowering process.

Figure 4. α,β-Unsaturated aldehydes unable to participate in the organocatalytic Mukaiyama-Michael reaction.

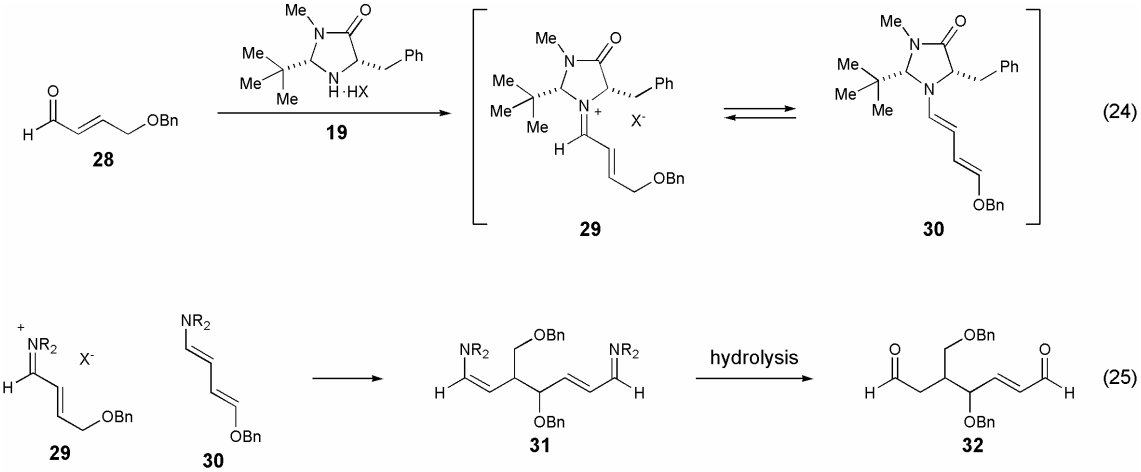


α,β-Unsaturated aldehydes with large β-substituents (**24**) also are not compatible with the organocatalytic Mukaiyama-Michael reaction (Figure 4). Large substituents at the β-position of α,β-unsaturated aldehydes are believed to retard the conjugate addition of the silyl ketene acetal through unfavorable steric interactions. This results in the acid catalyzed hydrolysis of the silyl ketene acetal becoming a much more competitive reaction pathway, thereby diminishing or obliterating yields. The α,β,γ,δ-unsaturated aldehyde **25** did not yield product, presumably due in part to this effect, and due in part to the greater stability and lesser reactivity of the iminium ion formed with the imidazolidinone catalyst **19**. Acrolein (**26**) and β-chloro acrolein (**27**) also do not participate in the organocatalytic Mukaiyama-Michael reaction.

Aldehydes with γ-oxygen substitution (**28**) also do not participate in the organocatalytic Mukaiyama-Michael reaction (Scheme 4). The acidity of the γ-hydrogens of the intermediate iminium ion **29** is high enough to allow the formation of a nucleophilic dienamine **30** (equation 24). The nucleophilic species **30** can then add to iminium ion **29** resulting in an overall dimerization of the starting aldehyde (**32**) after

hydrolysis of the intermediate **31** (equation 25). This process out competes the conjugate addition of the silyl ketene acetal yielding dimer of the starting aldehyde (**32**) and the thioester resulting from hydrolysis of the starting silyl ketene acetal.

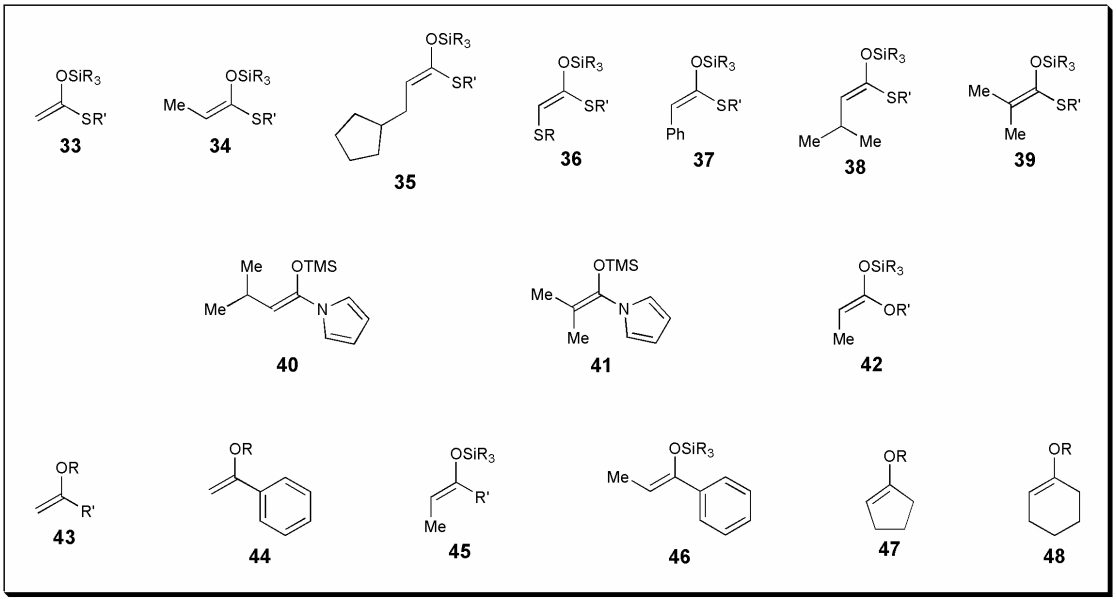
Scheme 4. Side reaction of γ-oxygenated α,β-unsaturated aldehydes under organocatalytic Mukaiyama-Michael reaction conditions.



While both *syn*- and *anti*-Mukaiyama-Michael products can be accessed based upon the proper choice of silyl ketene acetal, many latent enolate equivalents examined were not competent substrates for this transformation (Figure 5). Silyl ketene acetals derived from thioacetates (**33**) and *E*-silyl ketene acetals derived from thiopropionates (**34**) are less nucleophilic than the corresponding *Z*-thiopropionate silyl ketene acetals.[42] These substrates did not prove nucleophilic enough to participate in the conjugate addition, and yielded primarily hydrolysis products under organocatalytic reaction conditions. Increasing the steric bulk on thioester-derived silyl ketene acetals (compounds **35**-**39**) diminished their nucleophilicity enough to inhibit conjugate addition under organocatalytic conditions.

A similar effect was observed with pyrrole-derived silyl ketene acetals (Figure 5). Increased steric bulk at the α-position of the acyl pyrrole-derived latent enolate equivalent (compounds **40** and **41**) decreases its nucleophilicity enough to inhibit the conjugate addition.

Figure 5. Latent enolate equivalents not able to participate in the organocatalytic Mukaiyama-Michael reaction.

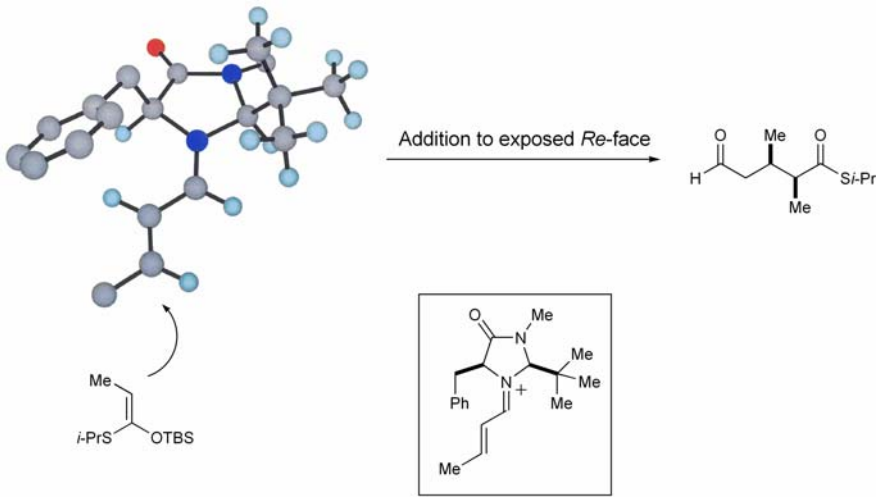


No ester-derived silyl ketene acetals (**42**) ever afforded conjugate addition product, and alkyl enol ethers and silyl enol ethers (**43**-**48**) were not competent substrates (Figure 5). Only latent enolate equivalents **46** and **47** yielded Mukaiyama-Michael adducts in significant yields, but these were in poor diastereo- and enantioselectivity.

Stereochemical Rationale

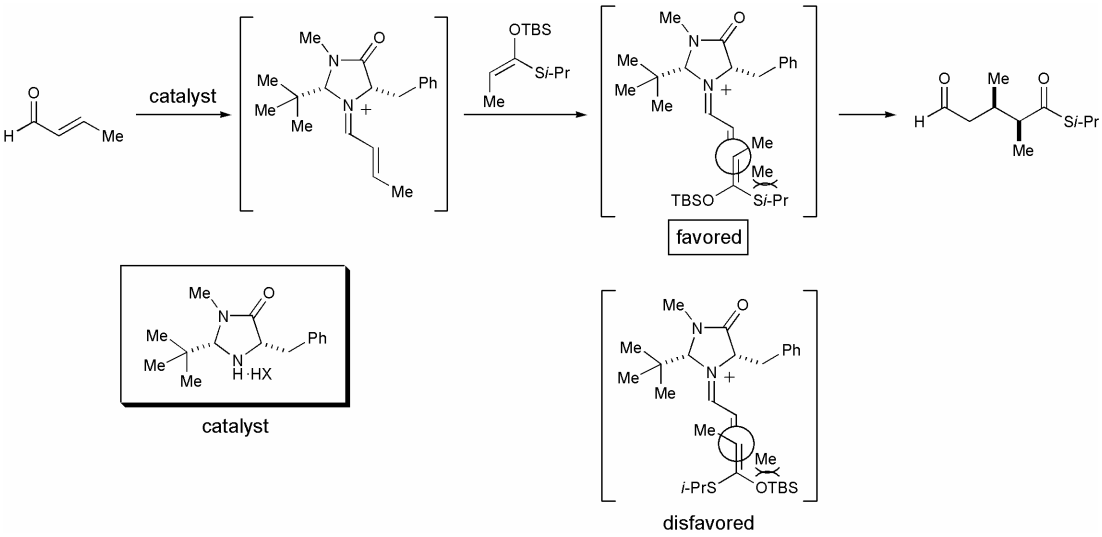
One of the great benefits of organocatalytic methodology is the ease with which it can be modeled using relatively simple computational methods. This simplicity in the calculation of intermediates allows accurate prediction of the selectivity of an organocatalytic process. The sense of enantioinduction observed in all cases is consistent with the conformation of a calculated iminium ion formed from imidazolidinone catalyst **19** and an α,β-unsaturated aldehyde (Scheme 5).[40] The steric bulk of the catalyst's *t*-butyl substituent controls the geometry of the iminium ion. The *E*-iminium ion and the position of the benzyl group combine to effectively shield the *Si*-face of the reactive olefin, and only allows conjugate addition to occur from the exposed *Re*-face. The *cis*-disposition of the *t*-butyl group relative to the benzyl group serves to reinforce this selectivity.

Scheme 5. Stereochemical rationale for the observed sense of enantioinduction.



The organocatalytic Mukaiyama-Michael reaction sets two stereocenters, so diastereoselectivity as well as enantioselectivity must be considered. The diastereoselectivity of the conjugate addition switches with the geometry of the nucleophile (Tables 9 and 10). The diastereoselectivity observed with each geometry of latent enolate equivalent is consistent with what has been observed in the literature for Lewis acid-catalyzed Mukaiyama-Michael reactions.[43]

Scheme 6. Stereochemical rationale for the observed diastereoselectivity with thioester-derived silyl ketene acetals.

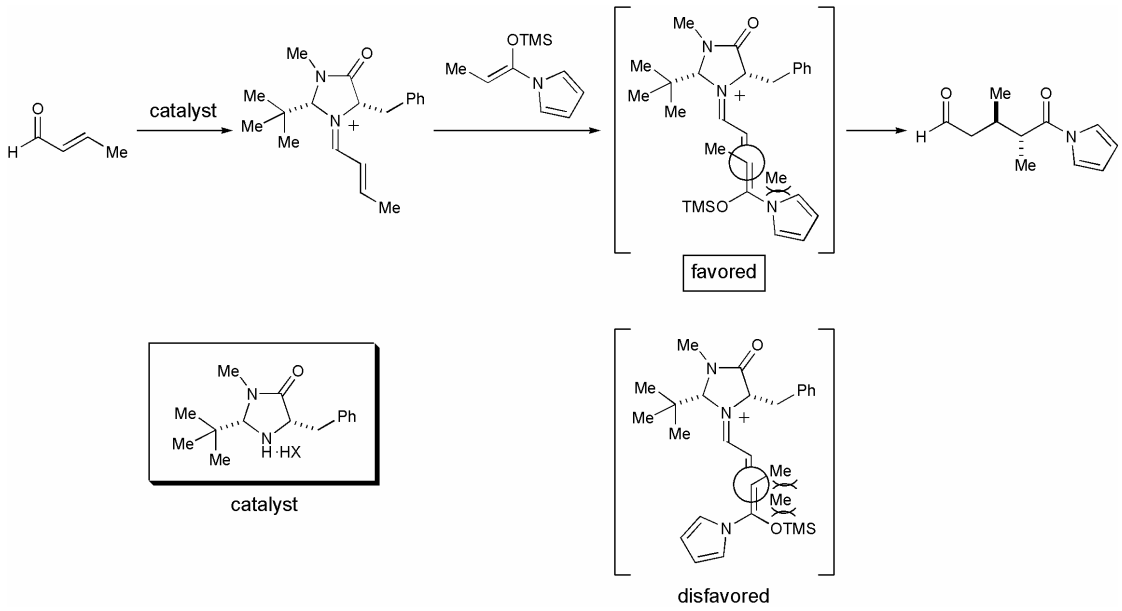


Organocatalytic Mukaiyama-Michael reactions between α,β-unsaturated aldehydes and *Z*-silyl ketene acetals derived from thioesters yield *syn*-products (Scheme 6). It is assumed that the conjugate addition of the latent enolate equivalent will occur through an open transition state. This is the case for Lewis acid catalyzed Mukaiyama-Michael reactions, and the same reasoning applies under organocatalytic conditions.[43] In an open transition state, approach of the nucleophilic olefin occurs anti-periplanar to the electrophilic olefin. Once the proper orientation between the reacting

olefins is established, minimization of steric interactions results in the prediction of the *syn*-product. In the favored transition state, the β-methyl substituent of the iminium ion is involved in two gauche interactions, one with the methyl group of the silyl ketene acetal, and one with the thioether of the silyl ketene acetal. There is also a weak gauche interaction between the *S*-isopropyl group of the silyl ketene acetal and the β-substituent of the aldehyde. In the disfavored transition state the methyl group of the silyl ketene acetal is involved in a gauche interaction with the iminium ion, and the large silyl group is involved in a gauche interaction with the β-methyl substituent of the iminium ion. The interaction between the silyl group and the β-methyl substituent is the dominating interaction, and it is of sufficient magnitude to favor the former transition state.

Organocatalytic Mukaiyama-Michael reactions between α,β-unsaturated aldehydes and *Z*-silyl ketene acetals derived from acyl pyrroles yield *anti*-products (Scheme 7). The olefin geometry for the silyl ketene acetal is designated (*Z*) for both thioester- and acyl pyrrole-derived silyl ketene acetals, but the relative configurations are opposite. Again, it is assumed that the conjugate addition of the latent enolate equivalent will occur through an open transition state.[43] In an open transition state, approach of the nucleophilic olefin occurs anti-periplanar to the electrophilic olefin. Once the proper orientation between the reacting olefins is established, minimization of steric interactions results in the prediction of the *anti*-product. In the favored transition state, the β-methyl substituent of the iminium ion is involved in only one gauche interaction with the relatively small, planar pyrrole ring. In the disfavored transition state, the same β-methyl substituent is involved in a gauche interaction with the large silyl group and the methyl group of the latent enolate equivalent.

Scheme 7. Stereochemical rationale for the observed diastereoselectivity with acyl pyrrole-derived silyl ketene acetals.



III. Conclusion

An asymmetric organocatalytic Mukaiyama-Michael reaction has been described herein. Using a chiral imidazolidinone salt, Mukaiyama-Michael adducts of α,β-unsaturated aldehydes and latent enolate equivalents can be accessed in good yields and selectivities. The organocatalytic Mukaiyama-Michael reaction has led to the development of a second generation imidazolidinone catalyst that demonstrates higher reactivity and selectivity than the catalyst developed for the organocatalytic Diels-Alder reaction. This new catalyst should allow the development of a greater number of organocatalytic transformations than possible with the original imidazolidinone catalyst.

IV. Experimental Section

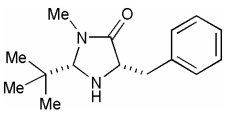
General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[44] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of prducts was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[45] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed be fluorescence quenching, *p*-anisaldehyde stain, or $KMnO_4$ stain.

^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively) or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported with chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) , integration, and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C, $CHCl_3$). Mass spectra were obtained from the California Institute of Technology Mass Spectrometer Facility. Gas chromatography was performed on Agilent 5890A and Hewlett-Packard 6890 Series gas chromatographs equipped with a split/splitless capillary injection system and flame ionization detectors using the following columns: J&C industries DB-1701 (30 m x 0.25 mm), Bodman Chiraldex Γ-

TA (30 m x 0.25 mm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254 nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

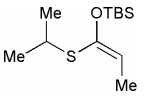
General procedure for the organocatalytic Mukaiyama-Michael reaction. A 1-dram vial with a magnetic stirrer was charged with the appropriate (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one salt (**19**), the appropriate solvent, H_2O, and α,β-unsaturated aldehyde. The solution was then stirred at room temperature for 5 min before being cooled to the desired temperature. The solution was stirred for 5 min before the appropriate silyl ketene acetal was added. The resulting mixture was maintained at the desired temperature until consumption of the silyl ketene acetal as determined by TLC. The reaction was then quenched by cold filtration through silica and purified by silica gel chromatography.

General procedure for the preparation of acyl oxazolidinone derivatives. An analytical quantity (approximately 10 mg) of the purified Mukaiyama-Michael adduct was oxidized to the corresponding acid according to the procedure previously described in the literature.[46] The crude acid was then coupled to 2-oxazolidinone according to the procedure previously described in the literature.[20] The resulting product was purified by silica gel chromatography (20-35% EtOAC/Hex).

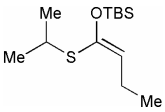


(2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (19). The title compound was prepared as previously described in the

literature.[47] All spectral data were in agreement with those previously reported. $[\alpha]_D$ = - 71.8 ° (free base).

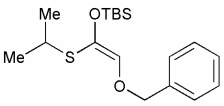


***tert*-Butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane.** The title compound was prepared from thiopropionic acid *S*-isopropyl ester according to the procedure described in the literature.[20] bp = 43 °C (160 mT); IR (CH_2Cl_2) 2960, 2930, 2860, 1634, 1473, 1463, 1364, 1256, 1152, 1110, 946, 853, 840, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (q, *J* = 6.8 Hz, 1H, vinyl), 3.30 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 1.68 (d, *J* = 6.8 Hz, 3H, methyl), 1.26 (d, *J* = 6.9 Hz, 6H, SCH(C**H**$_3)_2$), 0.93 (s, 9H, Si$(CH_3)_2$C(C**H**$_3)_3$), 0.17 (s, 6H, Si(C**H**$_3)_2$C$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 110.2, 35.0, 25.9, 25.7, 23.2, 18.1, 13.7, -4.7; HRMS (FAB peg) exact mass calcd for M+H ($C_{12}H_{27}OSiS$) requires *m/z* 247.1552, found *m/z* 247.1540.

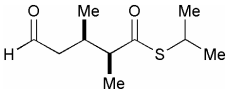


***tert*-Butyl-(1-isopropylsulfanyl-but-1-enyloxy)-dimethyl-silane.** The title compound was prepared from thiobutyric acid *S*-isopropyl ester according to the procedure described in the literature.[20] The title compound was purified by removing all volatiles from the crude product by distillation (15 mT, 100 °C bath). IR (CH_2Cl_2) 2960, 2931, 2896, 2860, 1627, 1472, 1463, 1363, 1256, 1151, 1130, 1112, 1063, 1006, 840, 781, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, *J* = 7.5 Hz, 1H, vinyl-H), 3.30 (septet, *J* = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 2.13 (app pentet, *J* = 7.7 Hz, 2H, C**H**$_2CH_3$), 1.51 (d, *J* = 6.9 Hz, 6H, SCH(C**H**$_3)_2$), 0.96-0.90 (m, 12H, SiC(C**H**$_3)_3$ and CH_2C**H**$_3$), 0.18 (s, 6H, Si(*t*-Bu)(C**H**$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 117.9, 34.8, 25.7, 23.2, 21.9, 18.1, 14.7, -4.7; HRMS (EI) exact mass calcd for ($C_{13}H_{28}OSiS$) requires

m/z 260.1630, found *m/z* 260.1625.

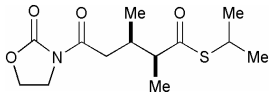


Z-(2-Benzyloxy-1-isopropylsulfanyl-vinyloxy)-*tert*-butyl-dimethylsilane. The title compound was prepared from benzyloxy-thioacetic acid *S*-isopropyl ester according to the procedure described in the literature.[20] The title product was isolated from the crude reaction mixture by filtration through triethylamine-treated silica (5% TEA/hexanes). IR (CH_2Cl_2) 2958, 2929, 2859, 1252, 1153, 839, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (m, 5H, ArH), 6.18 (s, 1H, vinyl-H), 4.70 (s, 2H, CH_2Ph), 3.19 (septet, J = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 1.19 (d, J = 6.6, 6H, SCH(C**H**$_3)_2$), 0.81 (s, 9H, Si(C(C**H**$_3)_3)(CH_3)_2$), 0.01 (s, 6H, Si(C$(CH_3)_3)$(C**H**$_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.4, 133.0, 128.5, 128.0, 127.9, 74.4, 35.6, 25.9, 23.4, 18.3, -4.4; HRMS (FAB) exact mass calcd for ($C_{18}H_{30}O_2SiS$) requires *m/z* 338.1736, found *m/z* 338.1747.

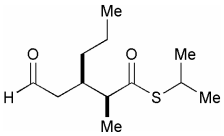


(2*S*, 3*R*)-2,3-Dimethyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 1). The title compound was prepared according to the general procedure from crotonaldehyde (124 μL, 1.5 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (0.14 mL, 0.50 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (41 mg, 0.10 mmol) in acetone (0.25 mL) and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 23 h. The resulting residue was purified by silica gel chromatography (10% ether/pentane) to provide the pure product as a colorless oil in 76% yield (77 mg, 0.38 mmol). 10:1 *syn*:*anti*, *Syn* isomer: IR (CH_2Cl_2) 2968, 1725, 1681, 1455, 1384, 1369, 1246, 965, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

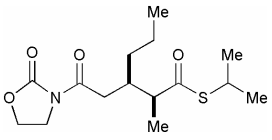
9.72 (dd, *J* = 2.5, 1.7 Hz, 1H, CHO), 3.62 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 2.58-2.38 (m, 2H, CHOC**H**$_2$), 2.34-2.22 (m, 1H, COC**H**(CH_3)C), 1.32-1.24 (m, 7H, CC**H**(CH_3)C and SCH(C**H**$_3)_2$), 1.14 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)), 0.96 (d, *J* = 6.6 Hz, 3H, CCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 201.7, 53.1, 48.8, 34.9, 31.3, 23.3, 23.2, 17.2, 14.5; HRMS (EI) exact mass calcd for M+H ($C_{10}H_{19}O_2S$) requires *m/z* 203.1106, found *m/z* 203.1106. $[\alpha]_D$ = + 34.1 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



(2*S*, 3*R*)-2,3-Dimethyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2970, 1780, 1697, 1685, 1388, 1219, 965 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, *J* = 8.0 Hz, 2H, OC**H**$_2$CH$_2$N), 4.01 (t, *J* = 8.2 Hz, 2H, OCH$_2$C**H**$_2$N), 3.61 (septet, *J* = 6.9 Hz, 1H, SC**H**$(CH_3)_2$), 3.16-2.36 (m, 4H, COC**H**$_2$C**H**(CH_3)C**H**(CH_3)CO), 1.29 (d, *J* = 1.9 Hz, 3H, SCH(C**H**$_3)(CH_3)$), 1.27 (d, *J* = 1.9 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 1.12 (d, *J* = 7.2 Hz, 3H, COCH(C**H**$_3$)C), 0.95 (d, *J* = 6.9 Hz, 3H, COCH$_2$CH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 172.3, 153.7, 62.2, 52.4, 42.7, 39.9, 34.7, 34.5, 32.4, 23.2, 16.2, 13.1; HRMS (FAB) exact mass calcd for ($C_{13}H_{22}NO_4S$) requires *m/z* 288.1270, found *m/z* 288.1264. $[\alpha]_D$ = + 37.1 °. Enantiomeric excess was determined by HPLC analysis(ODH and ODH guard, 3% isopropanol in hexanes, 1 mL/min); (2*R*, 3*S*) isomer t_r = 89.3 min and (2*S*, 3*R*) isomer t_r = 100.0 min.

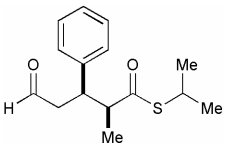


(2*S*, 3*R*)-2-Methyl-3-(2-oxo-ethyl)hexanethioic acid *S*-isopropyl ester (Table 9, entry 2). The title compound was prepared according to the general procedure from 2-hexenal (157 μL, 1.35 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (0.13 mL, 0.45 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (37 mg, 0.090 mmol) in acetone (0.225 mL) and H_2O (8.1 μL, 0.45 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (3% EtOAc/Hex) to provide the pure product as a colorless oil in 62% yield (64 mg, 0.28 mmol). 6:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2961, 2931, 1725, 1680, 1463, 1367, 965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.0 Hz, 1H, CHO), 3.62 (septet, *J* = 6.8 Hz, 1H, SC**H**$(CH_3)_2$), 2.72-2.64 (m, 1H, COC**H**(CH_3)C), 2.52 (ddd, *J* = 17.1, 5.4, 2.0 Hz, 1H, CH**H**CHO), 2.43-2.32 (m, 2H, C**H**(*n*-Pr)C**H**HCHO), 1.43-1.22 (m, 10H), 1.14 (d, *J* = 6.8 Hz, 3H, COCH(C**H**$_3$)C), 0.89 (t, *J* = 6.8, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 202.1, 51.0, 46.2, 36.1, 34.9, 33.8, 23.3, 23.1, 20.1, 14.9, 14.5; HRMS (EI) exact mass calcd for ($C_{12}H_{22}O_2S$) requires *m/z* 230.1341, found *m/z* 230.1341. $[\alpha]_D$ = + 29.5 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



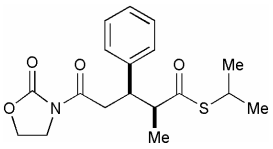
(2*S*, 3*R*)-2-Methyl-3-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-hexanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2962, 1782, 1697, 1684, 1387, 1223, 1197, 958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, *J* = 7.2 Hz, 2H, OC**H**$_2$CH$_2$N), 4.02 (t, *J* = 7.7 Hz, 2H, OCH$_2$C**H**$_2$N), 3.61 (septet, *J* =

6.9 Hz, 1H, SC**H**$(CH_3)_2$), 3.12-2.70 (m, 3H COC$\mathbf{H}_2$CH(*n*-Pr)C**H**(CH_3)CO), 2.52-2.40 (m, 1H, CCH(*n*-Pr)C), 1.40-1.20 (m, 10H, SCH(C$\mathbf{H}_3)_2$ and C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_3$), 1.11 (d, *J* = 6.9 Hz, 3H, CH(C$\mathbf{H}_3$)CO), 0.87 (t, *J* = 6.6 Hz, 3H, CH_2C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 172.8, 153.7, 62.2, 50.6, 42.8, 37.1, 37.0, 34.6, 32.9, 23.3, 23.1, 20.3, 14.4, 13.1; HRMS (FAB) exact mass calcd for ($C_{15}H_{26}NO_4S$) requires *m/z* 316.1583, found *m/z* 316.1581. $[\alpha]_D$ = + 30.3 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 3% isopropanol in hexanes, 1 mL/min); (2*S*, 3*R*) isomer t_r = 25.3 min and (2*R*, 3*S*) isomer t_r = 27.0 min; *Anti* diastereomers t_r = 30.2 and 33.5 min.

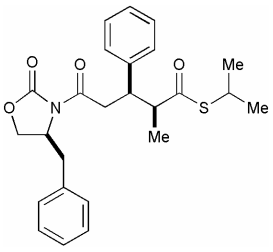


(2*S*, 3*R*)-2-Methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester (Table 9, entry 3). The title compound was prepared according to the general procedure from cinnamaldehyde (76 μL, 0.60 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (95 μL, 0.40 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (33 mg, 0.080 mmol) in acetone (0.20 mL), cyclohexane (14 μL), and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (5% EtOAc/Hex) to provide the pure product as a colorless oil in 50% yield (52 mg, 0.20 mmol). 20:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2967, 1725, 1677, 1453, 963, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (t, *J* = 2.2 Hz, 1H, CHO), 7.34-7.14 (m, 5H, ArH), 3.67 (septet, *J* = 6.6 Hz, 1H, SC**H**$(CH_3)_2$), 3.44 (dt, *J* = 10.4, 7.1 Hz, 1H CHPh), 2.86-2.78 (m, 1H, COC**H**(CH_3)C), 2.77 (dd, *J* = 7.1, 1.7 Hz, 2H, CHOC$\mathbf{H}_2$), 1.33 (d, *J* = 6.7 Hz, 3H, SCH(C$\mathbf{H}_3$)(CH_3)), 1.31 (d, *J* = 6.0 Hz, 3H, SCH(CH_3)(C$\mathbf{H}_3$)), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 200.8, 140.8, 128.9, 128.2, 127.4, 54.0, 48.3,

43.6, 35.1, 23.3, 23.2, 17.2; HRMS (EI) exact mass calcd for ($C_{15}H_{20}O_2S$) requires *m/z* 264.1184, found *m/z* 264.1182. $[\alpha]_D$ = + 49.6 °. Diastereomer ratios were determined by GLC analysis (Γ-TA column, 130 °C isotherm, 1 mL/min); *syn* diastereomer t_r = 33.1 min and *anti* diastereomer t_r = 36.6 min. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

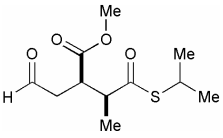


(2*S*, 3*R*)-2-Methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-3-phenyl-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2968, 2929, 1780, 1699, 1678, 1455, 1388, 1272, 1224, 1041, 968, 760, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H, ArH), 4.35-4.15 (m, 2H, OC**H**$_2$CH$_2$N), 3.95-3.45 (m, 5H), 3.10 (app dd, *J* = 16.2, 3.0 Hz, 1H, COC**H**HCH(Ph)), 2.88 (ddd, *J* = 17.1, 9.9, 7.2 Hz, 1H, COCH**H**CH(Ph)), 1.33 (d, *J* = 6.9 Hz, 3H, SCH(C**H**$_3$)(CH$_3$)), 1.30 (d, *J* = 7.2 Hz, 3H, SCH(CH$_3$)(C**H**$_3$)), 0.93 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 171.2, 153.4, 141.2, 128.4, 128.3, 126.9, 61.9, 53.3, 44.4, 42.4, 39.4, 34.7, 23.0, 22.9, 17.0; HRMS (FAB) exact mass calcd for M+H ($C_{18}H_{24}NO_4S$) requires *m/z* 350.1426, found *m/z* 350.1421. $[\alpha]_D$ = + 34.7 °. Enantiomeric excess was determined by HPLC analysis (ODH and ODH guard, 6% isopropanol in hexanes, 1 mL/min); (2*S*, 3*R*) isomer t_r =47.6 min and (2*R*, 3*S*) isomer t_r = 54.3 min.



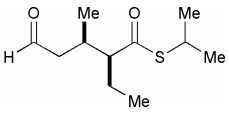
(2*S*, 3*R*)-5-((4*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methyl-5-oxo-3-phenyl-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure.

IR (CH_2Cl_2) 2971, 2928, 1782, 1702, 1674, 1454, 1388, 1355, 1213, 954, 761, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.03 (m, 10H, ArH), 4.38-4.26 (m, 1H, OCH_2C**H(**Bn)N), 3.95 (dd, *J* = 9.0, 2.7 Hz, OC**H**HCH(Bn)N), 3.90-3.36 (m, 4H), 3.13-3.00 (m, 2H, CH_2Ph), 2.90-2.76 (m, 1H, COC**H**HCH(Ph)), 2.55 (dd, *J* = 13.4, 9.8 Hz, 1H, COCH**H**CH(Ph)), 1.29 (d, *J* = 6.9 Hz, 3H, SCH(C**H**$_3$)(CH_3)), 1.25 (d, *J* = 6.9 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 0.88 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 171.1, 153.3, 141.1, 135.3, 129.4, 128.9, 128.5, 128.4, 127.2, 127.0, 66.0, 55.1, 53.5, 44.7, 39.7, 37.7, 34.7, 31.2, 23.0, 22.9, 17.0; HRMS (FAB) exact mass calcd for M+H ($C_{25}H_{30}NO_4S$) requires *m/z* 440.1896, found *m/z* 440.1882. $[\alpha]_D$ = + 64.5 °. The title compound was recrystallized (THF/hexanes) to afford x-ray quality crystals for XRD analysis (see Appendix 1).



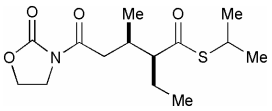
(2*S*, 3*R*)-3-Isopropylsulfanylcarbonyl-2-(2-oxo-ethyl)-butyric acid methyl ester (Table 9, entry 4). The title compound was prepared according to the general procedure from 4-oxo-but-2-enoic acid methyl ester (43 mg, 0.38 mmol), *tert*-butyl-1-(isopropylsulfanyl-propenyloxy)-dimethylsilane (59 μL, 0.25 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (20 mg, 0.050 mmol) in acetone (0.125 mL) and H_2O (4.5 μL, 0.25 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (CH_2Cl_2) to provide the pure product as a colorless oil in 73% yield (45 mg, 0.18 mmol). 4:1 *syn*:*anti*, *Syn* 91% ee. *Syn* isomer: IR (CH_2Cl_2) ; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (app s, 1H, CHO), 3.71 (s, 3H, CO_2CH_3), 3.64 (septet, *J* = 6.9 Hz, 1H, SC**H**(CH_3)$_2$), 3.19 (qd, *J* = 7.7, 3.7 Hz, 1H COC**H**(CH_3)C), 3.01-2.87 (m, 2H, $COCH_2C$), 2.64 (td, *J* = 3.2, 0.5 Hz, 1H,

$(CH_2)(CH)C\mathbf{H}CO_2CH_3$), 2.60 (d, *J* = 6.9 Hz, 6H, $SCH(C\mathbf{H}_3)_2$), 1.20 (d, *J* = 6.9 Hz, 3H, $COCH(C\mathbf{H}_3)C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 199.4, 173.3, 52.1, 48.2, 43.2, 41.0, 34.9, 22.9, 22.8, 15.8; HRMS (EI) exact mass calcd for M+H ($C_{11}H_{19}O_4S$) requires *m/z* 247.1004, found *m/z* 247.1015. $[\alpha]_D$ = + 0.74 °. Diastereomer ratios and enantiomeric excess were determined by GLC analysis (Γ-TA column, 130 °C isotherm, 1 mL/min); (2*S*, 3*R*) isomer t_r =29.1 min, (2*R*, 3*S*) isomer t_r = 30.4 min, and *anti* isomer t_r = 33.0 min.

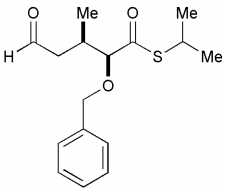


(2*S*, 3*R*)-2-Ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 5). The title compound was prepared according to the general procedure from crotonaldehyde (25 μL, 0.30 mmol), *tert*-Butyl-(1-isopropylsulfanyl-but-1-enyloxy)-dimethyl-silane (29 μL, 0.10 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TCA **19** (8.0 mg, 0.020 mmol) in diethyl ether (0.050 mL), benzyl methyl ether (5.0 μL), and H_2O (1.8 μL, 0.10 mmol) at -78 °C. The solution was stirred until the reaction was judged to be complete by GLC analysis (DB-1701 column, 70 °C, 25 °C/min gradient, 1 mL/min); benzyl methyl ether t_r = 3.75 min, 2-ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester t_r = 6.40 min. A yield of 76% was determined by comparison of the peak areas of benzyl methyl ether and 2-ethyl-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester. 4:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2968, 1727, 1678, 1461 990, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 2.4, 1.3 Hz, 1H, CHO), 3.66 (septet, *J* = 6.9 Hz, 1H, $SC\mathbf{H}(CH_3)_2$), 2.62-2.20 (m, 3H, $CHOC\mathbf{H}_2CH(CH_3)C\mathbf{H}(Et)COS(i\text{-}Pr)$), 1.77-1.46 (m, 3H, $CH_2C\mathbf{H}(CH_3)C$ and $C\mathbf{H}_2CH_3$), 1.30 (d, *J* = 6.9 Hz, 6H, $SCH(C\mathbf{H}_3)_2$), 0.99 (d, *J* = 6.1 Hz, 3H, $CH_2CH(C\mathbf{H}_3)C$), 0.91 (t, *J* = 7.5 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6,

201.8, 60.5, 48.3, 48.2, 34.7, 30.3, 23.0, 22.9, 17.9, 11.8; HRMS (EI) exact mass calcd for M-H ($C_{11}H_{19}O_2S$) requires *m/z* 215.1106, found *m/z* 215.1114. $[\alpha]_D$ = + 2.0 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

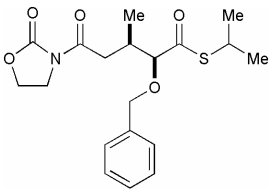


(2*S*, 3*R*)-2-Ethyl-3-methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentanethioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 94% ee. *Syn* isomer: IR (CH_2Cl_2) 2966, 1779, 1682, 1456, 1386, 1223, 1109, 1042, 990, 827, 761, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.2 Hz, 2H, OC**H$_2$**CH$_2$N), 4.02 (t, *J* = 7.4 Hz, 2H, OCH$_2$C**H$_2$**N), 3.65 (septet, *J* = 6.9 Hz, 1H, SC**H**(CH$_3$)$_2$), 3.03-2.85 (m, 1H, CHCOS(*i*-Pr)), 2.53-2.36 (m, 2H, COCH$_2$), 1.80-1.40 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 6H, SCH(C**H$_3$**)$_2$), 0.99 (d, *J* = 6.6 Hz, 3H, CHC**H$_3$**), 0.90 (t, *J* = 7.2 Hz, 3H, CH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 172.3, 153.4, 62.0, 60.0, 42.5, 39.6, 34.6, 31.8, 26.3, 22.9, 21.8, 17.1, 12.0; HRMS (EI) exact mass calcd for M + H ($C_{14}H_{24}NO_4S$) requires *m/z* 302.1426, found *m/z* 302.1440. $[\alpha]_D$ = + 20.7 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 1% ethanol in hexanes, 1 mL/min); *syn* isomers t_r = 54.2 and 68.4 min and *anti* isomers t_r = 48.6 and 49.8 min.



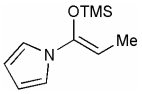
(2*S*, 3*R*)-2-Benzyloxy-3-methyl-5-oxo-pentanethioic acid *S*-isopropyl ester (Table 9, entry 6). The title compound was prepared according to the general procedure from crotonaldehyde (85 μL, 1.0 mmol), *Z*-(2-benzyloxy-1-isopropylsulfanyl-vinyloxy)-*tert*-butyl-dimethylsilane (0.12

mL, 0.34 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TFA **19** (25 mg, 0.068 mmol) in CH_2Cl_2 (0.17 mL) and H_2O (6.1 μL, 0.34 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as a colorless oil in 82% yield (82 mg, 0.28 mmol). >20:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 2966, 1724, 1676, 1456, 1124, 1087, 1059, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (t, *J* = 2.2 Hz, 1H, CHO), 7.40-7.28 (m, 5H, ArH), 4.81 (d, *J* = 11.5 Hz, 1H, PhC**H**HO), 4.35 (d, *J* = 11.5 Hz, 1H, PhCH**H**O), 3.86 (d, *J* = 4.4 Hz, 1H, COCH(OBn)C), 3.65, (septet, *J* = 7.1 Hz, 1H, SC**H**$(CH_3)_2$), 2.66-2.45 (m, 2H, CHOCH**H**C**H**(CH_3)C), 2.31 (ddd, *J* = 16.5, 6.6, 1.6 Hz, 1H, CHOC**H**HC), 1.34 (d, *J* = 3.3 Hz, 3H, SCH(C**H**$_3$)(CH_3)), 1.32 (d, *J* = 3.3 Hz, 3H, SCH(CH_3)(C**H**$_3$)), 0.98 (d, *J* = 7.1 Hz, 3H, CHOCH$_2$CH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 201.2, 137.1, 128.6, 128.4, 128.2, 86.8, 73.9, 47.4, 32.3, 25.9, 23.3, 23.2, 15.0; HRMS (FAB) exact mass calcd for M+H ($C_{16}H_{23}O_3S$) requires *m/z* 295.1368, found *m/z* 295.1376. $[\alpha]_D$ = + 77.1 °. Diastereomer ratios were determined by ^1H NMR or GLC analysis (DB-1701 column, 70 °C, 25 °C/min gradient to 280 °C isotherm, constant flow 1 mL/min); *syn* isomer t_r = 9.02 min and *anti* isomer t_r = 9.38 min. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

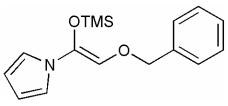


(2*S*, 3*R*)-2-Benzyloxy-3-methyl-5-oxo-5-(2-oxo-oxazolidin-3-yl)-pentantthioic acid *S*-isopropyl ester. The title compound was prepared according to the general procedure. *Syn* 90% ee. *Syn* isomer: IR (CH_2Cl_2) 2968, 2929, 2869, 1782, 1697, 1677, 1479, 1455, 1388, 1312, 1223, 1102, 1042, 755, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H, ArH), 4.86

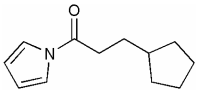
(d, *J* = 11.5 Hz, 1H, OC**H**HCH$_2$N), 4.35 (d, *J* = 8.2 Hz, 2H, CH$_2$Ph), 4.32 (d, *J* = 5.0 Hz, 1H, OCH**H**CH$_2$N), 4.00 (d, *J* = 3.9 Hz, 1H, COCH(OBn)C), 3.97-3.71 (m, 2H, OCH$_2$C**H$_2$**N), 3.65 (septet, *J* = 7.1 Hz, 1H, SCH(Me)$_2$), 2.94 (dd, *J* = 17.6, 8.2 Hz, 1H, COC**H**HC), 2.79 (dd, *J* = 17.6, 5.5 Hz, 1H, COCH**H**C), 2.63-2.52 (m, 1H, CHMe), 1.34 (d, *J* = 2.2 Hz, 3H, SCH(C**H$_3$**)(CH$_3$)), 1.32 (d, *J* = 2.8 Hz, 3H, SCH(CH$_3$)(C**H$_3$**)), 0.98 (d, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.2, 171.8, 155, 137.5, 128.7, 128.5, 127.9, 85.9, 73.9, 62.1, 42.5, 38.5, 34.1, 33.4, 23.3, 23.3, 14.6; HRMS (EI) exact mass calcd for ($C_{19}H_{27}NO_5S$) requires *m/z* 380.1532, found *m/z* 380.1537. $[\alpha]_D$ = +63.6 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 10% isopropanol in hexanes, 1 mL/min); *syn* isomers t_r = 25.1 and 31.9 min.



1-(1-Trimethylsilanyloxy-propenyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[48] All spectral data were in agreement with those previously reported.

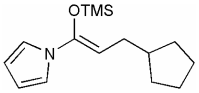


1-(2-Benzyloxy-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[20] All spectra data were in agreement with those previously reported.

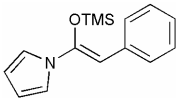


3-Cyclopentyl-1-pyrrol-1-yl-propan-1-one. The title compound was prepared from pyrrole and 3-cyclopentyl-propionyl chloride according to the procedure described in the literature.[48] Analytical data: bp = 125-130 °C (2 mm Hg); IR (CH_2Cl_2) 2948, 2866, 1717, 1469, 1331, 1277, 1118, 1071, 921, 740 cm^{-1}; ^{1}H

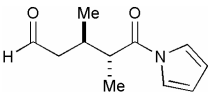
NMR (300 MHz, $CDCl_3$) δ 7.32 (t, *J* = 2.2 Hz, 2H, ArH), 6.28 (t, *J* = 2.2 Hz, 2H, ArH), 2.82 (dd *J* = 8.5, 7.4 Hz, 2H, $COCH_2$), 1.90-1.40 (m, 9H), 1.25-1.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 119.0, 113.0, 39.6, 33.9, 32.5, 32.4, 30.9, 25.6, 25.2; HRMS (EI) exact mass calcd for ($C_{12}H_{27}NO$) requires *m/z* 191.1310, found *m/z* 191.1310.



1-(3-Cyclopentyl-1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole. The title compound was prepared from 3-cyclopentyl-1-pyrrol-1-yl-propan-1-one (X) according to the procedure described in the literature.[48] IR (CH_2Cl_2) 2953, 2869, 1723, 1682, 1470, 1312, 1254, 1200, 1087, 921, 847, 801, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (t, *J* = 2.4 Hz, 2H, ArH), 6.17 (t, *J* = 2.4 Hz, 2H, ArH), 4.71 (t, *J* = 7.4 Hz, 1H, vinyl), 2.88-2.62 (m, 1H), 2.49-2.31 (m, 1H), 1.95-1.35 (m, 7H), 1.30-1.00 (m, 2H), 0.35 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.7, 119.0, 108.8, 107.5, 40.2, 32.9, 32.7, 32.4, 25.2, 25.0, 2.1; HRMS (EI) exact mass calcd for M + H ($C_{15}H_{26}NOSi$) requires *m/z* 264.1784, found *m/z* 264.1772.

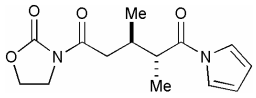


1-(2-Phenyl-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole. The title compound was prepared as described in the literature.[20] All spectral data were in agreement with those previously reported.

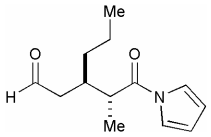


(3*R*, 4*R*)-Dimethyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 1). The title compound was prepared according to the general procedure from crotonaldehyde (124 μL, 1.5 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (0.104 mL, 0.50 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-

one·TCA **19** (41 mg, 0.10 mmol) in toluene (1.0 mL) and H_2O (9.0 μL, 0.50 mmol) at -78 °C for 21 h. The resulting residue was purified by silica gel chromatography (30% ether/pentane) to provide the pure product as an oil in 92% yield (89 mg, 0.46 mmol). 1:17 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 2971, 1717, 1468, 1369, 1272, 1104, 1074, 909, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (dd, *J* = 2.4, 1.1 Hz, 1H, CHO), 7.30 (t, *J* = 2.4 Hz, 2H, ArH), 6.29 (t, *J* = 2.1 Hz, 2H, ArH), 3.13 (app pentet, *J* = 6.4, 1H, COC**H**(CH_3)C), 2.69-2.48 (m, 2H, CHOC**H**HC**H**(CH_3)C), 2.31 (ddd, *J* = 16.8, 8.2, 2.1 Hz, 1H, CHOCH**H**C), 1.23 (d, *J* = 6.9 Hz, 3H, COCH(C**H**$_3$)), 1.08 (d, *J* = 6.9 Hz, 3H, CCH(C**H**$_3$)C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 173.3,119.0, 113.3, 46.7, 42.4, 30.8, 18.5, 14.1; HRMS (EI) exact mass calcd for ($C_{11}H_{15}NO_2$) requires *m/z* 193.1103, found *m/z* 193.1101. $[\alpha]_D$ = - 36.6 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

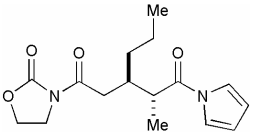


(2*R* 3*R*)-2,3-Dimethyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 83% ee. All spectral data were consistent with those reported in the literature.[20]



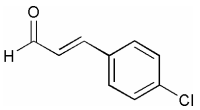
(3*R*)-3-((1*R*)-1-Methyl-2-oxo-2-pyrrol-1-yl-ethyl)-hexanal (Table 10, entry 2). The title compound was prepared according to the general procedure from 2-hexenal (157 μL, 1.35 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole **X** (94 μL, 0.45 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-

imidazolidin-4-one·DNBA (41 mg, 0.090 mmol) in DME (0.225 mL) and H_2O (8.1 μL, 0.45 mmol) at -40 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 56% yield (55 mg, 0.25 mmol). 1:4 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 2959, 1715, 1469, 1273, 1103, 1073, 910, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.3 Hz, 1H, CHO), 7.46 (t, *J* = 2.4 Hz, 2H, ArH), 6.31 (t, *J* = 2.4 Hz, 2H, ArH), 3.33 (septet, *J* = 5.3 Hz, 1H, SC**H**$(CH_3)_2$), 2.71-2.32 (m, 4H, CHOC**H**$_2$C**H**(*n*-Pr)C**H**(CH_3)), 1.46-1.10 (m, 7H, C**H**$_2$C**H**$_2CH_3$ and CHC**H**$_3$), 0.85 (t, *J* = 6.9 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 173.5, 119.3, 113.2, 45.8, 40.4, 35.1, 32.1, 20.1, 14.0, 13.2; HRMS (EI) exact mass calcd for ($C_{13}H_{19}NO_2$) requires *m/z* 221.1416, found *m/z* 221.1419. $[\alpha]_D$ = + 0.42 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

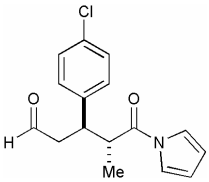


(2*R*, 3*R*)-2-Methyl-5-(2-oxo-oxazolidin-3-yl)-3-propyl-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 93% ee. *Anti* isomer: IR (CH_2Cl_2) 2959, 1785, 1700, 1685, 1467, 1391, 1334, 1311, 1265, 1225, 1119, 1100, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 2.6, 2.2 Hz, 2H, ArH), 6.30 (dd, *J* = 2.6, 2.2 Hz, 2H, ArH), 4.43 (t, *J* = 8.4 Hz, 2H, OC**H**$_2CH_2$N), 4.03 (t, *J* = 8.4 Hz, 2H, OCH_2C**H**$_2$N), 3.43 (qd, *J* = 6.6, 4.4 Hz, 1H, COC**H**(Me)C), 3.13 (dd, *J* = 18.5, 9.2 Hz, 1H, COC**H**HC), 3.00 (dd, *J* = 18.0, 4.4 Hz, 1H, COCH**H**C), 2.55-2.43 (m, 1H, CCCH(*n*-Pr)), 1.47-1.21 (m, 4H, C**H**$_2$C**H**$_2CH_3$), 1.18 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 0.82 (t, *J* = 6.6 Hz, 3H, CH_2C**H**$_3$); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 173.7, 173.0, 153.7, 119.7, 113.2, 62.3, 42.8, 40.6, 37.0, 36.6, 31.5, 20.5, 14.2, 11.7; HRMS (FAB) exact mass calcd for ($C_{16}H_{23}N_2O_4$) requires *m/z* 307.1658, found *m/z* 307.1653; $[\alpha]_D$ = -18.5 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 6% isopropanol in hexanes, 1 mL/min); (2*S*, 3*S*) isomer t_r = 38.6 min and (2*R*, 3*R*) isomer t_r = 41.6 min; *syn* isomers t_r = 29.4 and 35.4 min.



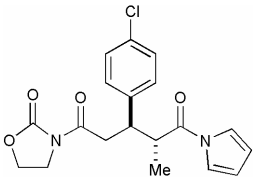
3-(4-Chlorophenyl)-propenal. The title compound was prepared as described in the literature.[49] All spectral data were in agreement with those previously reported.



(3*R*, 4*R*)-3-(4-Chlorophenyl)-4-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 3). The title compound was prepared according to the general procedure from 3-(4-chlorophenyl)-propenal (117 mg, 0.70 mmol), 1-(1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (73 μL, 0.35 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TFA **19** (25 mg, 0.070 mmol) in THF (0.70 mL), cyclohexane (49 μL), and H_2O (6.3 μL, 0.35 mmol) at -60 °C for 23 h. The resulting residue was purified by silica gel chromatography (20% EtOAc/Hex) to provide the pure product as an oil in 74% yield (75 mg, 0.26 mmol). 1:3 *syn:anti*. *Anti* isomer: IR (CH_2Cl_2) 1718, 1492, 1468, 1411, 1368, 1325, 1298, 1271, 1111, 1092, 1074, 1014, 917, 894, 827, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (t, *J* = 1.8 Hz, 1H, CHO), 7.36 (br s, 2H, ArH), 7.30 (d, *J* = 8.5 Hz, 2H, ArH), 7.14 (d, *J* = 8.5 Hz, 2H, ArH), 6.34 (t, *J* = 2.1 Hz, 2H, ArH), 3.66 (td, *J* = 9.1, 5.3 Hz, 1H, CHAr), 3.42-3.32 (m, 1H,

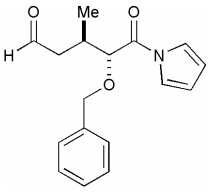
$CHCONR_2$), 2.89-2.71 (m, 2H, C**H**$_2$CHO), 1.33 (d, *J* = 7.0, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 172.9, 138.8, 133.2, 129.5, 129.0, 119.0, 113.8, 47.7, 43.3, 42.2, 16.7; HRMS (EI) exact mass calcd for ($C_{16}H_{17}NO_2Cl$) requires *m/z* 290.0948, found *m/z* 290.0951; $[\alpha]_D$ = -28.0 °. Diastereomer ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

Syn isomer: IR (CH_2Cl_2) 2976, 1720, 1710, 1492, 1467, 1409, 1366, 1323, 1275, 1094, 1074, 1014, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (dd, *J* = 2.1, 1.2 Hz, 1H, CHO), 7.26-7.13 (m, 6H, ArH), 6.25 (t, *J* = 2.4 Hz, 2H, ArH), 3.74 (ddd, *J* = 9.7, 8.2, 5.0 Hz, 1H, CHAr), 3.43 (dt, *J* = 15.2, 7.0 Hz, 1H, $CHCONR_2$), 2.98 (ddd, *J* = 17.3, 4.7, 1.2, 1H, C**H**HCHO), 2.85 (ddd, *J* = 17.3, 9.7, 2.1, 1H, CH**H**CHO), 1.33 (d, *J* = 7.0, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 172.7, 140.1, 133.3, 129.5, 129.2, 119.1, 113.8, 45.7, 43.9, 41.7, 15.6; HRMS (EI) exact mass calcd for ($C_{16}H_{17}NO_2Cl$) requires *m/z* 290.0948, found *m/z* 290.0945; $[\alpha]_D$ = +16.2 °.



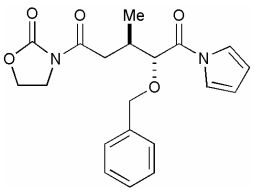
(2*R*, 3*R*)-3-(4-Chloro-phenyl)-2-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 98% ee. *Anti* isomer: IR (CH_2Cl_2) 1777, 1703, 1468, 1389, 1271, 1225, 1092, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 2.1 Hz, 2H, ArH), 7.29 (d, *J* = 8.4 Hz, 2H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 6.34 (t, *J* = 2.1 Hz, 2H, ArH), 4.31 (t, *J* = 8.4 Hz, 2H, OC**H**$_2$CH$_2$), 3.94-3.72 (m, 3H, CH_2C**H**$_2$N and CHAr), 3.57-3.37 (m, 2H, COC**H**(CH_3)C and COC**H**HC), 3.16 (dd, *J* = 17.3, 5.1 Hz, 1H, COCH**H**C), 1.06 (d, *J* = 7.2 Hz, 3H, CH_3);

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 170.9, 153.5, 139.3, 132.9, 129.8, 128.8, 119.1, 113.7, 62.1, 43.3, 43.0, 42.2, 39.5, 16.8; HRMS (FAB) exact mass calcd for M+H ($C_{19}H_{20}N_2O_4Cl$) requires *m/z* 375.1112, found *m/z* 375.1110. $[\alpha]_D$ = - 12.4 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 15% isopropanol in hexanes, 1 mL/min); (2*R*, 3*R*) isomer t_r = 30.4 min and (2*S*, 2*S*) isomer t_r = 34.7 min.

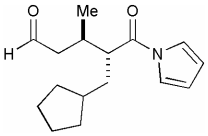


(3*R*, 4*R*)-4-Benzyloxy-3-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 4). The title compound was prepared according to the general procedure from crotonaldehyde (87 μL, 1.05 mmol), 1-(2-benzyloxy-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole (97 μL, 0.35 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TBA **19** (38 mg, 0.070 mmol) in THF (0.175 mL) and H_2O (6.3 μL, 0.35 mmol) at -78 °C for 22 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 69% yield (69 mg, 0.24 mmol). 1:42 *syn*:*anti*. A*nti* isomer: IR (CH_2Cl_2) 1720, 1469, 1318, 1295, 1099, 1076, 745, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (t, *J* = 1.6 Hz, 1H, CHO), 7.43-7.05 (m, 7H, ArH), 6.20-6.05 (m, 2H, ArH), 4.48 (d, *J* = 11.4 Hz, 1H, OC**H**HPh), 4.22 (d, *J* = 11.4 Hz, 1H, OCH**H**Ph), 4.05 (d, *J* = 7.7 Hz, 1H, COCH(OBn)C), 2.62-2.41 (m, 2H, CHOC**H**$_2$), 2.28 (td, *J* = 8.5, 1.6 Hz, 1H, CH_2C**H**(CH_3)CH), 0.85 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 169.5, 136.3, 128.5, 128.3, 128.3, 119.5, 113.5, 83.9, 72.6, 47.3, 32.3, 16.8; HRMS (EI) exact mass calcd for ($C_{17}H_{19}NO_3$) requires *m/z* 285.1365, found *m/z* 285.1358.

$[\alpha]_D$ = - 39.8 °. Diastereomer ratios and enantiomeric excess were determined by HPLC analysis of the corresponding acyl oxazolidinone.

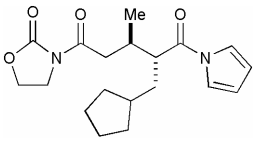


(2*R*, 3*R*)-2-Benzyloxy-3-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure.[20] All spectral data were in agreement with those previously reported.

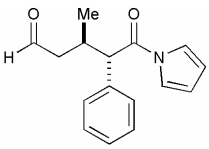


(3*R*, 4*R*)-4-Cyclopentylmethyl-3-methyl-5-oxo-5-pyrrol-1-yl-pentanal (Table 10, entry 5). The title compound was prepared according to the general procedure from crotonaldehyde (99 μL, 1.2 mmol), 1-(3-cyclopentyl-1-trimethylsilanyloxy-propenyl)-1*H*-pyrrole (0.11 mL, 0.40 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TBA **19** (43 mg, 0.080 mmol) in CH_2Cl_2 (0.10 mL), toluene (0.10 mL), and H_2O (7.2 μL, 0.40 mmol) at -78 °C for 24 h. The resulting residue was purified by silica gel chromatography (10% EtOAc/Hex) to provide the pure product as a yellow oil in 68% yield (71 mg, 0.27 mmol). 1:10 *syn*:*anti*. A*nti* isomer: IR (CH_2Cl_2) 2951, 1709, 1467, 1273, 1073, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.5 Hz, 1H, CHO), 7.34 (br s, 2H, ArH), 6.35-6.15 (m, 2H ArH), 3.34-2.92 (m, 1H), 2.7-1.8 (m, 3H), 1.78-1.36 (m, 9H), 1.16-0.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 173.2, 119.1, 113.5, 47.4, 47.3, 38.2, 35.5, 33.3, 33.1, 32.3, 31.0, 25.1, 18.0; HRMS (EI) exact mass calcd for ($C_{16}H_{23}NO_2$) requires *m/z* 261.1729, found *m/z* 261.1724. $[\alpha]_D$ = - 14.8 °. Diastereomer ratios were determined by ^1H NMR

analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.

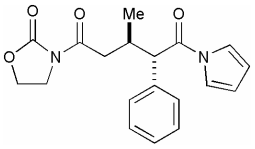


(2*R*, 3*R*)-2-Cyclopentylmethyl-3-methyl-5-(2-oxo-oxazolidin-3-yl)-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. A*nti* 88% ee. *Anti* isomer: IR (CH_2Cl_2) 2950, 2868, 1780, 1703, 1467, 1388, 1270, 1222, 1112, 1073, 1041, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (br s, 2H, ArH), 6.30 (t, *J* = 2.1 Hz, 2H, ArH), 4.39 (t, *J* = 8.0 Hz, 2H, OC**H**$_2$CH$_2$N), 3.99 (t, *J* = 8.2 Hz, 2H, OCH$_2$C**H**$_2$N), 3.23 (ddd, *J* = 10.4, 5.9, 3.7 Hz, 1H, COC**H**(CH$_2$*c*-penyl)CH), 3.12 (dd, *J* = 17.0, 5.1 Hz, 1H, COC**H**HCH(CH$_3$)C), 2.80 (dd, *J* = 17.3, 8.0 Hz, 1H, COCH**H**CH(CH$_3$)C), 2.58-2.42 (m, 1H, CH$_2$C**H**(CH$_3$)C), 2.10-0.84 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.1, 153.4, 119.2, 113.2, 62.0, 47.1, 42.5, 38.6, 38.3, 35.8, 33.3, 32.6, 32.4, 25.2, 25.1, 17.8; HRMS (EI) exact mass calcd for ($C_{19}H_{26}N_2O_4$) requires *m/z* 346.1893, found *m/z* 346.1894. $[\alpha]_D$ = -8.0 °. Enantiomeric excess was determined by HPLC analysis (ODH and OD guard, 15% ethanol in hexanes, 1 mL/min); *anti* isomers t_r = 10.8 and 15.2 min.



(3*R*, 4*S*)-3-Methyl-5-oxo-4-phenyl-5-pyrrol-1-yl-pentanal (Table 10, entry 6). The title compound was prepared according to the general procedure from crotonaldehyde (97 μL, 1.2 mmol), 1-(2-phenyl-1-trimethylsilanyloxy-vinyl)-1*H*-pyrrole **X** (99 μL, 0.39 mmol), and (2*S*, 5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one·TfOH (31 mg, 0.078 mmol) in $CHCl_3$ (0.195 mL) and H_2O (7.0 μL, 0.39 mmol) at -65 °C for 24 h. The resulting residue was purified by silica gel

chromatography (10% EtOAc/Hex) to provide the pure product as an oil in 78% yield (78 mg, 0.31 mmol). 1:3 *syn*:*anti*. *Anti* isomer: IR (CH_2Cl_2) 1709, 1470, 1288, 914, 474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (app br s, 1H, CHO), 7.40-7.20 (m, 7H, ArH), 6.25-6.20 (m, 2H, ArH), 4.12 (d, *J* = 9.3 Hz, 1H, CHPh), 3.10-2.88 (m, 1H, $CH_2C\mathbf{H}(CH_3)C$), 2.67 (app dd *J* = 16.5, 3.3 Hz, 1H, CHOC**H**HC), 2.49-2.35 (m, 1H, CHOCH**H**C), 0.85 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 201.2, 136.5, 129.2, 128.4, 128.1, 119.4, 113.5, 56.2, 49.2, 32.2, 17.9; HRMS (FAB) exact mass calcd for M+H ($C_{16}H_{18}NO_2$) requires *m/z* 256.1338, found *m/z* 256.1349. $[\alpha]_D$ = - 0.51 °. Diastereomer ratios were determined by ^1H NMR analysis. Enantiomeric excess was determined by conversion to the corresponding acyl oxazolidinone.



(2*S*, 3*R*)-3-Methyl-5-(2-oxo-oxazolidin-3-yl)-2-phenyl-1-pyrrol-1-yl-pentane-1,5-dione. The title compound was prepared according to the general procedure. *Anti* 87% ee. *Anti* isomer: IR (CH_2Cl_2) 1778, 1705, 1469, 1388, 1270, 1116, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.18 (m, 7H, ArH), 6.25-6.15 (m, 2H, ArH), 4.45-3.70 (m, 5H), 3.02-2.90 (m, 1H, COC**H**HC), 2.67 (dd, *J* = 17.0, 7.5 Hz, 1H, COCH**H**C), 1.29-1.18 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 170.4, 136.8, 129.0, 128.7, 127.9, 119.3, 113.2, 62.0, 56.2, 42.4, 40.2, 33.0, 19.1; HRMS (EI) exact mass calcd for ($C_{19}H_{20}N_2O_4$) requires *m/z* 340.1423, found *m/z* 340.1434. $[\alpha]_D$ = + 0.76 °. Enantiomeric excess was determined by HPLC analysis (AD and AD guard, 10% ethanol in hexanes, 1 mL/min); *anti* isomers t_r = 20.1 and 37.0 min and *syn* isomers t_r = 23.2 and 28.5 min.

V. References

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