Chapter 1

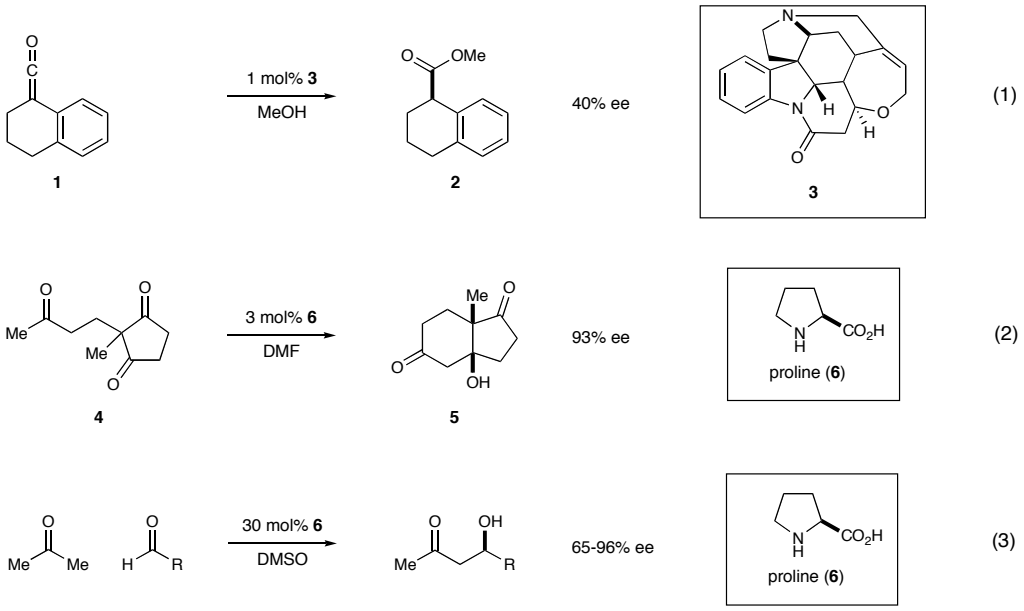
Enantioselective Organocatalysis

I. Introduction

Over the last 50 years, the need for single enantiomer molecules has driven great advances in the field of enantioselective catalysis. This growth has resulted in a wide variety of asymmetric organometallic catalysts that provide synthetic chemists with the tools to perform asymmetric oxidations, reductions, cycloadditions, conjugate additions, and σ-bond activation reactions.[1,2] The importance of enantioselective metal catalysis has been recognized by awarding the 2001 Nobel Prize in Chemistry to William S. Knowles,[3,4] Ryoji Noyori,[5,6] and K. Barry Sharpless[7] for their landmark work in this field.

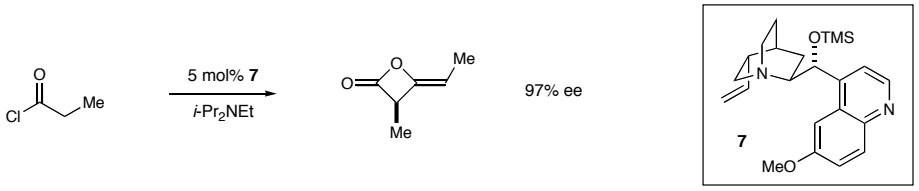
In contrast to organometallic catalysts, there are fewer asymmetric transformations catalyzed by organic molecules. The lack of organic catalysts (organocatalysts) is underscored by the fact that organic molecules are generally insensitive to air and moisture, precluding the need for expensive and time-consuming inert reaction conditions used in transition metal catalysis. Moreover, nature provides a multitude of enantiopure organic compounds such as α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates from which to develop organocatalysts. Organometallic catalysts are generally synthesized from these building blocks, although utilizing the chiral pool directly would prove to be more cost-effective and efficient. Along with these practical considerations, studying the relatively unexplored field of organic catalysis, or organocatalysis, should provide the opportunity to investigate new modes of reactivity and selectivity.

Interestingly, there are reports of organocatalysts as early as 1912 by Bredig, in which modest enantioselectivities were achieved for alkaloid-catalyzed cyanohydrin synthesis.[8] Much later, Pracejus reported the development of an organocatalyzed asymmetric ketene methanolysis reaction.[9,10] The presence of 1 mol% of **3** catalyzed the methanolysis of phenyl-□-*o*-trimethyleneketene (**1**) to generate the methyl ester **2** in 40% ee (eq 1). Another early example of asymmetric organocatalysis is the proline (**6**) catalyzed Robinson annulation of the symmetrical triketone **4** to provide the bicycle **5** in high levels of enantioselectivity (eq 2).[11,12] This reaction known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction though widely used for natural product synthesis,[13] remained relatively under-studied until List and co-workers developed the first intermolecular version of this aldol reaction in 2000 (eq 3).[14]



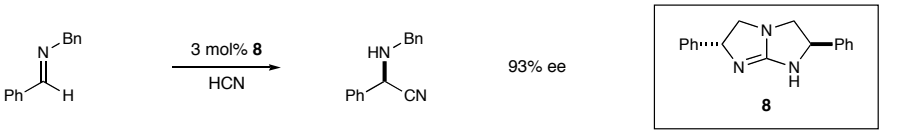
Building on Pracejus' precedence, many contemporary researchers have utilized nucleophilic organic catalysts to perform enantioselective cycloadditions, halogenations, Baylis-Hillman, acylations, and cyanations reactions.[15] In this class of catalysts, the

Cinchona alkaloids and their derivatives have been the most widely used (eq 4, ketene dimerization).[16]



(4)

Other examples of highly enantioselective organocatalysts include the enantioselective hydrocyanation catalyst developed by Corey[17] and Jacobsen[18,19] (eq 5), the highly enantioselective epoxidation catalysts developed by the groups of Shi,[20,21] Yang,[22,23] and Denmark[24] (eq 6), and the quaternary ammonium salts developed by Corey,[25] O'Donnell,[26] and Maruoka[27,28] for phase transfer catalysis (eq 7). Although each of these systems allows for the synthesis of enantioenriched products, they share the limitation in that they catalyze a single transformation.



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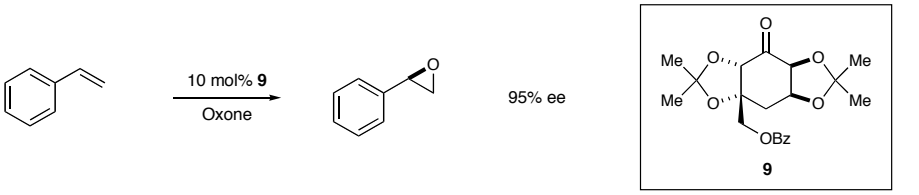

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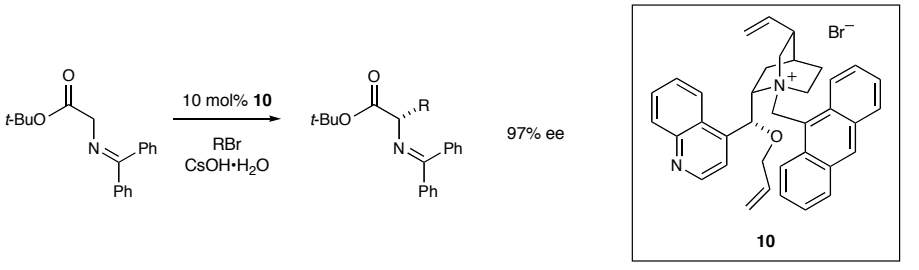


(7)

Organometallic complexes have been highly successful due to their mechanism of activation being applicable to a range of transformations.[29] In contrast, the activation

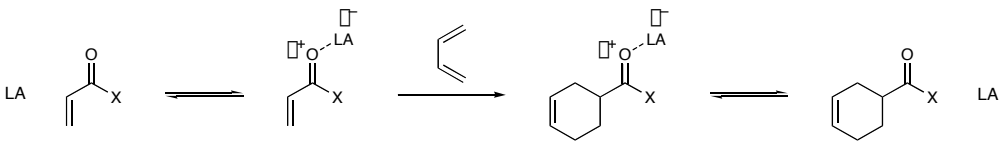
method of most of the organocatalysts were only applicable to single transformations. Therefore, our group became interested in developing a strategy of activation of organic molecules by organic catalysts that could encompass a wide scope of synthetic transformations.

II. Design of a General Approach to Enantioselective Organocatalysis

LUMO-Lowering Catalysis

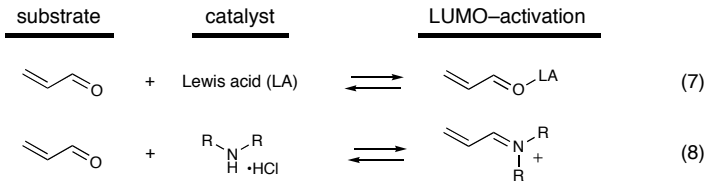
Lewis acids have found broad use in asymmetric catalysis for a variety of organic transformations through activation of both conjugated and isolated π-systems toward nucleophilic attack. The mechanism of Lewis acid catalysis occurs by reversible binding of the Lewis acid to the electrophile substrate resulting in redistribution of π-electrons toward the electropositive metal center (Scheme 1). This electronic redistribution lowers the energetic potential of the lowest unoccupied molecular orbital (LUMO) (eq 7), resulting in an increased susceptibility toward combination with the highest occupied molecular orbital (HOMO) of a reaction partner. Following bond formation, lability of the Lewis acid-product bond allows for catalyst turn-over, permitting further iterations of the catalytic cycle (Scheme 1).

Scheme 1. Lewis acid (LA) catalysis



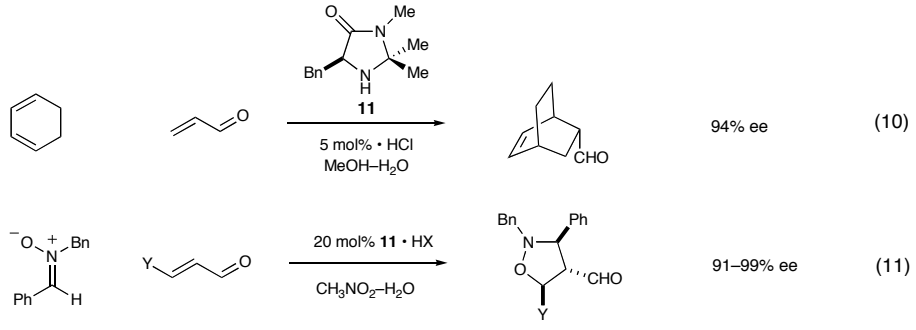
Two important features of Lewis acid catalysis is the kinetically labile association with the electrophile and the redistribution of electron density, which our group

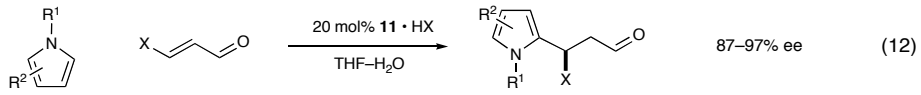
recognized could be emulated by simple secondary amines. The reversible condensation of a secondary amine with an α,β-unsaturated aldehyde to form a positively charged iminium ion achieves these two important features of Lewis acid catalysis (eq 8). Moreover, if enantiopure secondary amines were used as catalysts, a new opportunity for enantioselective catalysis would be realized.



Chiral Imidazolidinone Catalysts

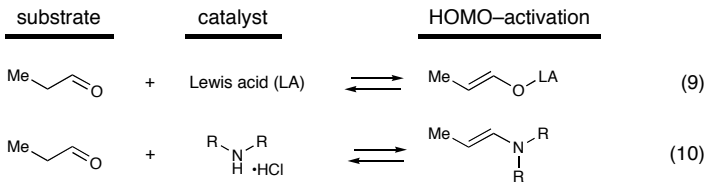
Iminium activation strategy was first demonstrated in the development of the first enantioselective, organocatalytic Diels-Alder cycloaddition (eq 10).[30] The imidazolidinone catalyst **11** imparts an enantiofacial bias to the conjugated π-system to produce Diels-Alder products in high levels of enantiomeric excess. Soon after this, iminium activation strategy was extended to nitrone cycloadditions (eq 11)[31] and to conjugate addition of pyrroles (eq 12).[32] The success of catalyzing three mechanistically different reactions held promise for further utilization of the imidazolidinone architecture for enantioselective organocatalysis of other traditional and non-traditional chemical transformations.





HOMO-Raising Catalysis

Lewis acids have also been used to activate substrates by a HOMO-raising activation mechanism to generate activated nucleophiles (eq 9). In a comparable manner, a secondary amine can emulate a similar electronic redistribution by means of reversible formation of an enamine complex. The HOMO of the resulting enamine is higher than its corresponding aldehyde (eq 10) and thus activated toward combination with the LUMO of an electrophile. This catalysis principle has been demonstrated for a variety of enantioselective organic transformations utilizing proline or one of its derivatives as the chiral secondary amine catalyst (eq 2,3).[11,12,14]



III. Summary of Thesis Research

The following chapters describe efforts toward general organocatalytic methodology that utilize these two forms of activation. Chapter 2 discusses the further development of the LUMO-lowering activation for the enantioselective Freidel-Crafts alkylations of heterocycles. Chapter 3 describes the extension of LUMO-lowering activation to an enantioselective Mukaiyama-Michael reaction for the construction of the □-butenolide architecture[33] and □-amino acids.[34] Chapters 4 and 5 detail the use of

HOMO-raising activation for the enantioselective synthesis of □-oxy[35] and □-chloroaldehydes.[36]

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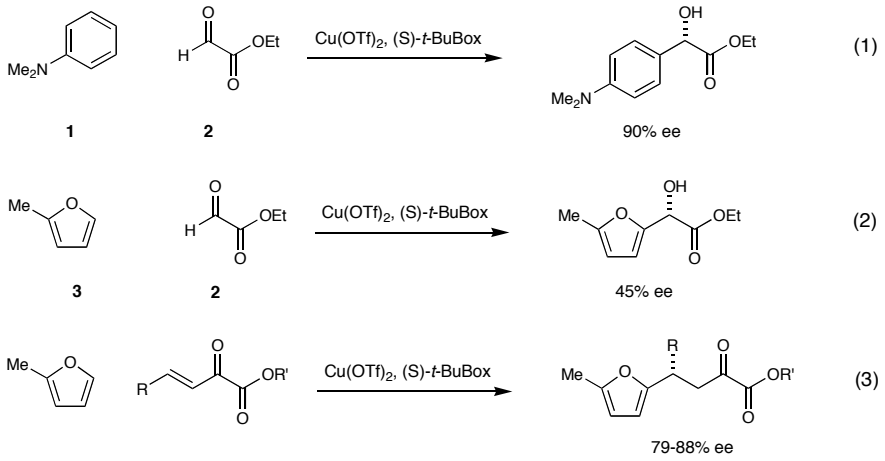
Chapter 2

Enantioselective Organocatalytic Friedel-Crafts Alkylation of Furans

I. Introduction

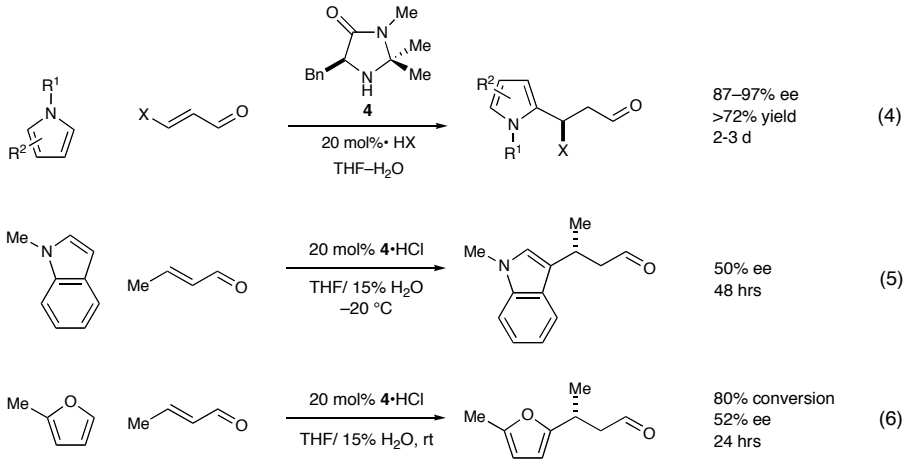
Enantioselective Friedel-Crafts Reactions

The Friedel-Crafts alkylation is one of the most widely used and studied reactions in organic chemeistry.[1,2] Surprisingly, there was only one example of an enantioselective catalytic variant prior to our research. The Jørgensen group described the first enantioselective Friedel-Crafts alkylation in which $Cu(OTf)_2$ (*S*)-*t*-butylbisoxazoline complex catalyzes the addition of dimethylaniline **1** (eq 1) and 2-methylfuran (**3**) (eq 2) to ethyl glyoxylate (**2**).[3] During our studies, the Jørgensen group extended this methodology to the enantioselective conjugate addition of furans (eq 3).[4] These processes were limited by the need for a bidentate chelating substrate, modest enantioselectivity, and extended reaction time.



Organocatalytic Friedel-Crafts Reactions

Following the development of the enantioselective conjugate addition of substitute pyrroles (eq 4)[5] employing the imidazolidinone **4**, Nick Paras in our laboratory had obtained modest preliminary results for the conjugate addition of other, less reactive heterocyclic aromatics such as *N*-methylindole (eq 5, 50% ee) and 2-methylfuran (eq 6, 52% ee). This chapter describes the further development and optimization of a highly enantioselective Friedel-Crafts alkylation of substituted furans with α,β-unsaturated aldehydes.



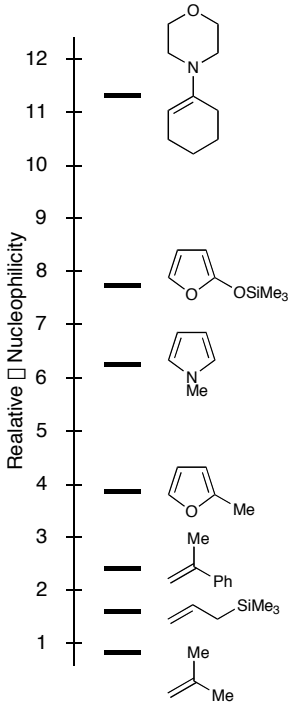
II. Results and Discussion

First Generation Imidazolidinone Catalyst

Low levels of enantioselectivity were achieved for the conjugate addition of substituted furans upon utilizing the conditions reported for the enantioselective conjugate additon of pyrroles (eq 4).[5] Under these conditions, THF is the bulk solvent and water (15% by volume) is utilized as a co-solvent to promote hydrolysis and facilitate catalyst turnover. The greater enantioselectivity obtained by pyrrole nucleophiles is due to pyrrole being greater than two orders of magnitude more nucleophilic than furan

(Figure 1).[6] This superior nucleophilicity facilitates greater reaction rate enabling further optimization by decreasing the temperature or adjusting other variables that may decrease the reaction rate, but increase the enantioselectivity.

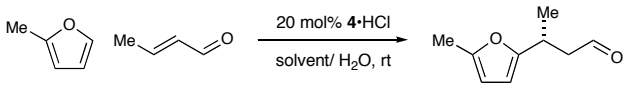
Figure 1. Mayr's study of the relative reactivity of nucleophilic π systems[6]



To overcome the inherent reactivity difference, we began to evaluate the effect of reaction variables for the conjugate addition of 2-methylfuran to crotonaldehyde with the HCl salt of catalyst **4** (Table 1). A survey of solvent demonstrated that dichloromethane (entry 4) gave low conversion while THF and *p*-dioxane gave moderate levels of enantioselectivity (entries 1 and 3, 57% ee). THF was selected for further studies because of its lower melting point (mp = –108 °C), as compared to *p*-dioxane (mp = 12 °C), thereby permitting lower temperature reactions. The catalyst's imidazolidinone architecture was next examined by varying the substituents around the heterocycle.

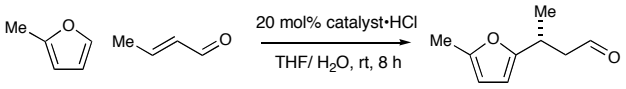
Various amine catalysts were evaluated, but most were less selective than catalyst **4** except for the cyclopentyl variant **5**. While the bulky cyclopentyl group decreased the rate of reaction, the enantioselectivity increased (Table 2).

Table 1. The effect of solvent on the alkylation of 2-methylfuran

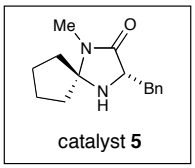


entry	solvent	% conversion	% ee
1	THF	87	57
2	Et_2O	68	4
3	dioxane	88	57
4	CH_2Cl_2	<5	n. d.
5	CH_3CN	84	27
6	toluene	48	0

Table 2. The effect of imidazolidone architecture on the alkylation of 2-methylfuran



entry	catalyst	% conversion	% ee
1	**4**	83	57
2	**5**	59	66

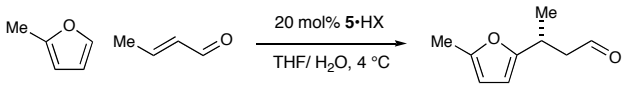


catalyst **5**

We next explored the effects of changing the acid cocatalyst (Table 3). The results in Table 3 show a correlation between increasing pK_a of the acid cocatalyst and an increase in enantioselectivity (entries 1-6). It is postulated that this orderly trend arises due to the enantioselectivity-determining step being the rearomatization of oxo-carbenium ion **7** to form the furan **8** (Scheme 1).[7] The oxo-carbenium ion **7** can participate in two possible processes: retro-conjugate addition of the furan to reform an α,β-unsaturated iminium ion **6**, or removal of proton H_a by the conjugate base of the acid

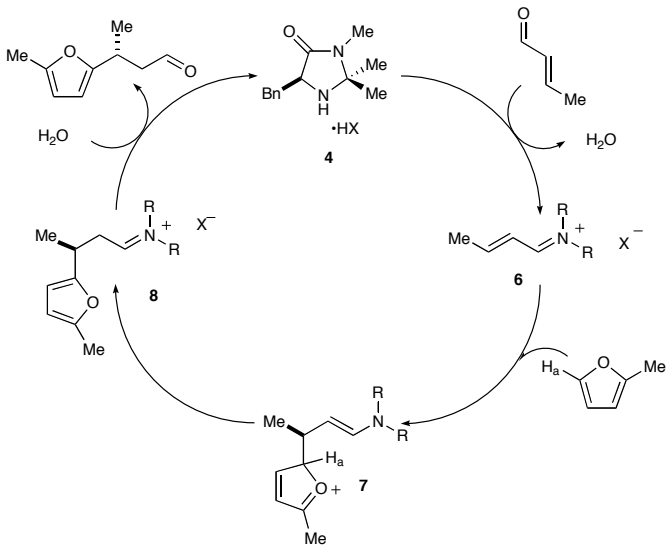
co-catalyst to reform the aromatic ring generating **8**. Stronger conjugate bases should favor the deprotonation over retro-conjugate addition affording greater levels of enantioselectivity.

Table 3. The effect of acid cocatalyst on the alkylation of 2-methylfuran



entry	HX	pK_a	% conversion	% ee
1	CNAcOH	2.47	34	71
2	DCA	1.35	51	70
3	DFA	1.34	50	71
4	TFA	0.52	83	68
5	TCA	0.51	72	69
6	HCl	-6.1	85	61

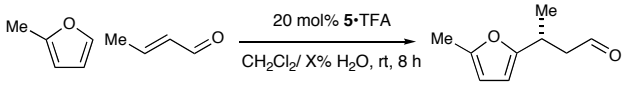
Scheme 1. Catalytic cycle of the organocatalytic Friedel-Crafts alkylation of furans



After substantial assessment of reaction parameters, it was discovered upon re-evaluation of solvent with TFA instead of HCl (Table 1, entry 4, <5% conversion) as the acid co-catalyst, that CH_2Cl_2 provided increased enantioselectivity (Table 4, entry 4, 71%

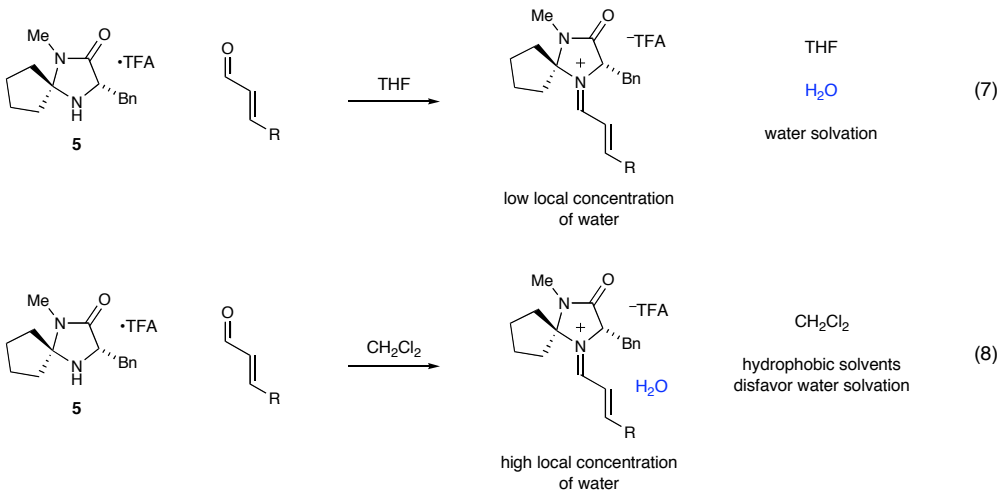
ee), highlighting the dependent nature of reaction variables in this organocatalytic system. The fact that water is predominantly immiscible in CH_2Cl_2 led us to explore the role of water on the reaction (Table 4). Varying the water content from 1% to 30% provided similar results (entries 2-6, 70-71% ee), although not adding water increased both conversion and enantioselectivity (entry 1, 66% conversion, 75% ee). Prior to these results (Table 4), it was thought that addition of water was necessary for iminium ion formation and catalyst turnover.[5,8,9]

Table 4. The effect of water on the alkylation of 2-methylfuran



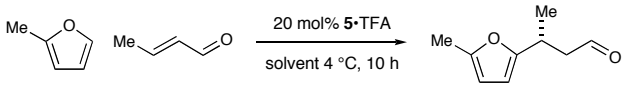
entry	% H_2O	% conversion	% ee
1	0	66	75
2	1	59	71
3	5	58	70
4	10	53	71
5	20	50	71
6	30	46	71

We propose that polar solvents efficiently solvate the water generated upon iminium ion formation, producing a low local concentration of water around the iminium ion hindering catalyst turnover (eq 7), and requiring additional water to facilitate catalyst turnover. Water solvation is unfavorable in hydrophobic solvents producing a close association between the charged catalyst iminium ion and water, affording facile catalyst turnover due to the high effective concentration of water around the iminium ion (eq 8).



A more extensive survey of nonpolar solvents revealed enantioselectivity increased with solvent of decreasing dielectric constant at the expense of conversion to the product (Table 5). We attributed the decrease in conversion with decreasing dielectric constant to the positively charged iminium ion being inadequately stabilized by the non-polar solvent leading to a reduced concentration of iminium ion in solution compared to more polar solvents. Chloroform was chosen for further studies because it provided increased enantioselectivity while still maintaining good reaction efficiency (Table 5, entry 2, 74% ee, 55% conversion).

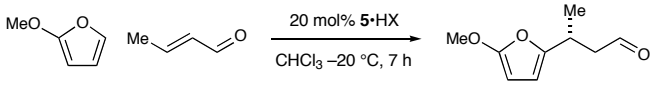
Table 5. The effect of non-polar solvents on the alkylation of 2-methylfuran



entry	solvent	□	% conversion	% ee
1	CH_2Cl_2	9.1	76	74
2	$CHCl_3$	4.8	55	78
3	C_2HCl_3	3.4	27	82
4	CCl_4	2.4	20	85
5	toluene	2.0	22	81
6	xylenes	2.4	18	81

2-Methoxyfuran had previously hydrolyzed under reaction conditions involving addition of water. Now with no additional water added to the reaction, 2-methoxyfuran was evaluated for the conjugate addition to crotonaldehyde with a variety of acid cocatalysts (Table 6). Although highly acidic cocatalysts still catalyzed the hydrolysis of 2-methoxyfuran (entries, 5-7, 0-33% conversion), less acidic cocatalysts provided for the first time high levels of enantioselectivity and good conversion (Table 6, entries 1-4, 90-93% ee, 72-76% conversion).

Table 6. The effect of cocatalyst on the alkylation of 2-methoxyfuran



entry	HX	pK_a	% conversion	% ee
1	CNAcOH	2.47	72	92
2	DBA	1.48	77	91
3	DCA	1.35	75	90
4	DFA	1.34	76	93
5	TFA	0.52	33	81
6	TCA	0.51	11	76
7	HCl	-6.1	0	n. d.

Second Generation Imidazolidinone Catalyst

At the time of these results, two of my colleagues, Chris Borths and Joel Austin, collaborated on the synthesis of a second-generation catalyst **9**.[10] This catalyst gave superior selectivity and an increased rate for the conjugate addition furans. The increased rate was attributed to removal of the eclipsing methyl group of catalyst **4**, further exposing the nucleophilic nitrogen of catalyst **9** (Figure 2). Moreover, furan nucleophiles that engage the activated iminium **10** must encounter a retarding interaction with the illustrated methyl substituent (Figure 3). In contrast, the reactive enantioface of iminium

ion **11** is free from steric obstruction and should exhibit increased rate of C–C bond formation. Greater *Si*-face coverage supplied by the *tert*-butyl substituent is credited for the increased selectivity of catalyst **9**.

Figure 2. Computation model of amine catalysts

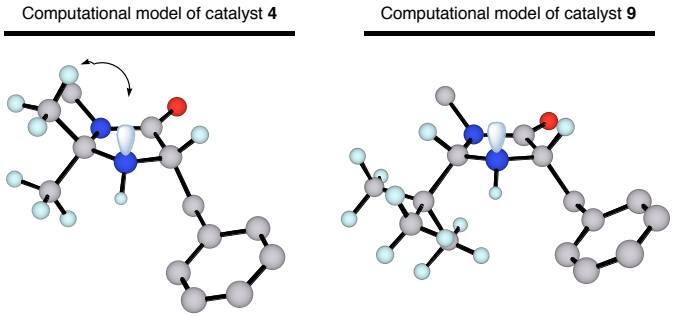
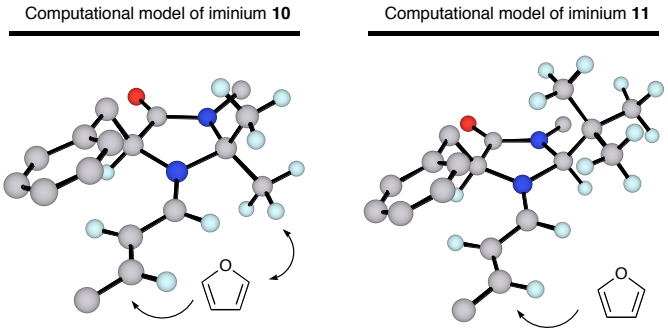


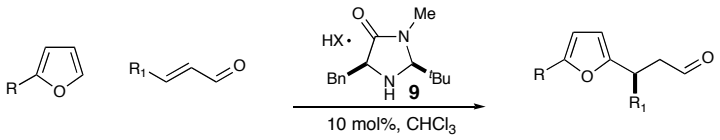
Figure 3. Computation model of catalysts iminium ions



We investigated the scope of the reaction of 2-methylfuran and various □,□-unsaturated aldehydes utilizing catalyst **9** (Table 7). Alkyl and aromatic substituents on the aldehyde are well tolerated, displaying excellent levels of enantioselectivity and chemical yield (entries 1-4, 93-96% ee, 82-95% yield). Aldehydes with electron-deficient moieties that destabilize iminium ion formation providing lower levels of an equilibrium concentration of iminium ion, also participate in conjugate addition reactions with excellent enantioselectivity and yield (entries 5-6, 95-97% ee, 92-85% yield).

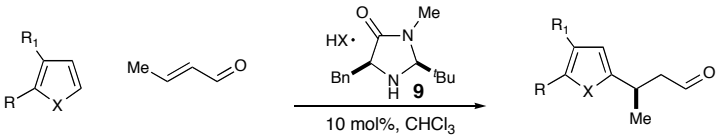
Unsubstituted furan participates in the conjugate addition reaction, as do alkyl and oxy substituted furans in excellent enantioselectivity (Table 8). The organocatalytic Friedel-Crafts alkylation reaction was also expanded to thiophenes with similarly high levels of enantioselectivity and yield (entry 5, 92% ee, 87% yield). This research constitutes the first highly enantioselective Friedel-Crafts alkylation of furans and thiophenes.

Table 7. Organocatalyzed conjugate addition of furans and thiophenes



entry	R	R_1	temp (°C)	time (h)	% yield	% ee
1	Me	Me	–20	11	82	93
2	Me	*n*-Pr	–20	26	90	93
3	OMe	*i*-Pr	–30	9	91	96
4	OMe	Ph	–50	6	95	94
5	Me	CH_2OBz	–20	22	92	97
6	Me	CO_2Me	–30	16	85	95

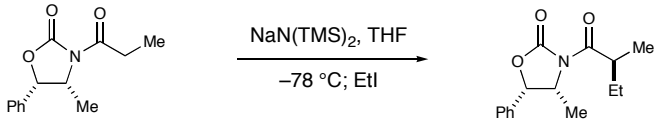
Table 8. Organocatalyzed conjugate addition of furans to □,□-unsaturated aldehydes

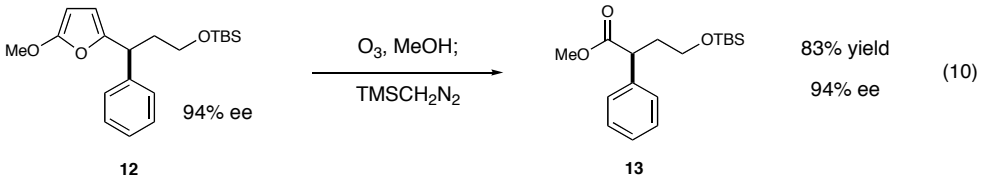


entry	R	R_1	X	HX	time (h)	% yield	% ee
1	H	H	O	TFA	8	78	93
2	Me	H	O	TFA	11	82	93
3	Me	Me	O	CNAcOH	41	74	98
4	OMe	H	O	DCA	5	78	95
5	OMe	H	S	TFA	23	87	92

Acyl Anion Equivalent

Surprisingly, with the tremendous success of enantioselective catalysis there are no approaches to the alkylation of enolates in an enantioselective catalytic fashion. Evans described a highly successful diastereoselective method to access a wide range of enolate alkylation products, though this process is limited by its use of chiral auxilaries (eq 9).[11] The enantioselective Friedel-Crafts alkylation of furans provides an opportunity to access a wide range of enolate alkylation products. Exposure of the Friedel-Crafts alkylation product **12** to ozone and workup with trimethylsilyl diazomethane affords an α-stereogenic ester **13** (eq 10). This methodology displays the utility of the enantioselective Friedel-Crafts alkylation furans as an acyl anion equivalent.





III. Conclusion

This chapter described the first highly enantioselective Friedel-Crafts alkylation of furans and thiophenes. The role of the water co-solvent was explored, determining that additional water was necessary with hydrophilic solvents and no additional water was needed when hydrophobic solvents were utilized. The development of amine catalyst **9** was required to achieve high levels of enantioselectivity and reaction

efficiency. Moreover, this technology provides a highly efficient enantioselective alternative to access enolate alkylation products.

IV. Experimental Section

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[12] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[13] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz, respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatography equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-DM or Γ-TA (30 m 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralcel AD column

(1.6 x 25 cm) and AD guard (1.6 x 5 cm), Chiralcel OD–H (1.6 x 25 cm) and OD guard (1.6 x 5 cm), or Chiralcel AS (1.6 x 25 cm) and AS guard (1.6 x 5 cm), as noted.

Procedures

General Procedure: To a 2-dram vial equipped with a magnetic stir bar and charged with (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one was added $CHCl_3$, associated acid and aldehyde, then placed in a bath at appropriate temperature. The solution was stirred for 10 min before the addition furan substrate in one portion. The resulting solution was stirred at constant temperature until reaction was determined to be complete by GLC conversion assay using benzyl methyl ether as an internal standard. The reaction mixture was then transferred cold through a silica gel plug with ether into a flask and carefully concentrated *in vacuo* with ice bath. The resulting residue was purified by silica gel chromatography (solvents noted) and fractions carefully concentrated *in vacuo* with ice bath to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

(*R*)-3-(5-Methyl-furan-2-yl)-butyraldehyde (Table 8, entry 1). Prepared according to the general procedure from (*E*)-crotonaldehyde (250 μL, 3.00 mmol), 2-methylfuran (90 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), trichloroacetic acid (7.7 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at –20 °C for 11 h to provide the title compound as a colorless oil (124.8 mg, 82% yield, 93% ee) after silica gel chromatography (10% Et_2O / petroleum ether). IR (film) 2968, 2926, 2884, 2823, 2729, 1726, 1566, 1218, 1021, 782.7 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) □ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 5.86 (d, *J* = 3.0 Hz, 1H, ArH), 5.83 (dd, *J* = 0.8, 3.0 Hz, 1H, ArH), 3.36 (m, 1H, C**H**CH_3), 2.75 (ddd, *J* = 1.9, 6.6, 16.8 Hz, 1H, C**H**$_2$), 2.54 (ddd, *J* = 1.9, 5.2, 16.8 Hz, 1H, C**H**$_2$), 2.23 (s, 3H, $ArCH_3$), 1.28 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 201.7, 156.5, 150.9, 106.0, 105.0, 49.6, 28.3, 19.4, 13.8; HRMS (CI) exact mass calcd for (M-1) ($C_9H_{12}O_3$) requires *m/z* 151.0759, found *m/z* 151.0754. [□]$_D$ = □2.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex □-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); *S* isomer t_r = 91.1 min and *R* isomer t_r = 91.7 min.

(*R*)-3-(5-Methyl-furan-2-yl)-hexanal (Table 8, entry 2). Prepared according to the general procedure from (*E*)-hexenal (348 μL, 3.00 mmol), 2-methylfuran (90 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), trichloroacetic acid (7.7 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at □20 °C for 26 h to provide the title compound as a colorless oil (161.6 mg, 90% yield, 93% ee) after silica gel chromatography (5% Et_2O / petroleum ether). IR (film) 3102, 2958, 2915, 2863, 2811, 2717, 1725, 1567, 1560, 1464, 1458, 1385, 1219, 1020, 947.4, 782.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 9.68 (t, *J* = 2.2 Hz, 1H, CHO), 5.86 (d, *J* = 3.0 Hz, 1H, ArH), 5.82- 5.79 (m, 1H, ArH), 3.21 (tt, *J* = 6.0, 8.2 Hz, 1H, CH_2C**H**CH_2), 2.69 (ddd, *J* = 2.5, 8.0, 16.8 Hz, 1H, C**H**$_2$), 2.54 (ddd, *J* = 2.2, 6.3, 16.8 Hz, 1H, C**H**$_2$), 2.21 (d, *J* = 1.1 Hz, 3H, $ArCH_3$), 1.71- 1.45 (m, 2H, CH_2Et), 1.33- 1.20 (m, 2H, CH_2Me), 0.87 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 201.9, 155.1, 150.8, 106.2, 106.0, 48.0, 36.5, 33.5, 20.6, 14.2, 13.8; HRMS (CI) exact mass calcd ($C_9H_{12}O_3$) requires *m/z* 180.1156, found *m/z* 180.1145. [□]$_D$ = +6.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was

determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (85 °C isotherm, 1 mL/min); *S* isomer t_r = 41.5 min and *R* isomer t_r = 45.2 min.

(*S*)-3-(5-Methoxy-furan-2-yl)-4-methyl-pentanal (Table 8, entry 3). Prepared according to the general procedure from (*E*)-4-methyl-2-pentenal (351 μL, 3.00 mmol), 2-methoxyfuran (92 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), dichloroacetic acid (8.2 μL, 0.10 mmol), and $CHCl_3$ (4.00 mL) at −30 °C for 9 h to provide the title compound as a colorless oil (160.2 mg, 91% yield, 96% ee) after silica gel chromatography (5% Et_2O / petroleum ether). IR (film) 2970, 2940, 2874, 2841, 2725, 1726, 1616, 1585, 1464, 1388, 1376, 1261, 1224, 1174, 1055, 1018, 967.5, 942.0, 738.4, 668.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (dd, *J* = 1.6, 2.5 Hz, 1H, CHO), 5.86 (dd, *J* = 0.8, 3.3 Hz, 1H, ArH), 4.99 (d, *J* = 3.0 Hz, 1H, ArH), 3.78 (s, 3H, OCH_3), 2.98 (dt, *J* = 5.2, 9.9 Hz, 1H, ArCH), 2.69 (ddd, *J* = 2.5, 9.9, 16.5 Hz, 1H, C**H**$_2$), 2.56 (ddd, *J* = 1.6, 5.2, 16.5 Hz, 1H, C**H**$_2$), 1.99- 1.82 (m, 1H, $CHMe_2$), 0.89 (d, *J* = 6.9 Hz, 3H, CH(**CH**$_3$)$_2$), 0.85 (d, *J* = 6.6 Hz, 3H, CH(**CH**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 160.8, 145.6, 107.8, 79.5, 57.9, 44.4, 40.0, 31.9, 20.4, 20.0; HRMS (CI) exact mass calcd ($C_9H_{12}O_3$) requires *m/z* 196.1099, found *m/z* 196.1098. $[\alpha]_D$ = +7.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (95 °C isotherm, 1 mL/min); *S* isomer t_r = 65.4 min and *R* isomer t_r = 69.9 min.

(*S*)-3-(5-Methoxy-furan-2-yl)-3-phenyl-propionaldehyde (Table 8, entry 4). Prepared according to the general procedure from (*E*)-cinnamaldehyde (378 μL, 3.00

mmol), 2-methoxyfuran (92 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), dichloroacetic acid (8.2 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at −50 °C for 6 h to provide the title compound as a colorless oil (218.6 mg, 95% yield, 95% ee) after silica gel chromatography (8% Et_2O / petroleum ether). IR (film) 3028, 2940, 2840, 2727, 1724, 1616, 1585, 1493, 1454, 1438, 1374, 1261, 1224, 1172, 1051, 1017, 966.2, 940.0, 748.6, 701.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.6 Hz, 1H, CHO), 7.36- 7.18 (m, 5H, PhH), 5.89 (ddd, *J* = 0.5, 1.1, 3.3 Hz, 1H, ArH), 5.03 (s, *J* = 3.3 Hz, 1H, ArH), 4.50 (t, *J* = 7.4 Hz, 1H, ArCHPh), 3.76 (s, 3H, OCH_3), 2.56 (ddd, *J* = 1.9, 8.0, 17.3 Hz, 1H, C**H**$_2$), 2.93 (ddd, *J* = 1.9, 7.1, 17.0 Hz, 1H, C**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 161.3, 145.7, 141.2, 128.9, 127.9, 127.3, 107.5, 79.8, 57.9, 48.3, 39.4; HRMS (CI) exact mass calcd ($C_9H_{12}O_3$) requires *m/z* 196.1099, found *m/z* 196.1098. $[\alpha]_D$ = +58.0 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using Chiralcel AD column (1.6 x 25 cm) and AD guard (1.6 x 5 cm) (3.0% ethanol / hexanes, 1 mL/mn); *S* isomer t_r = 41.3 min and *R* isomer t_r = 50.9 min.

(*S*)-Benzoic acid 2-(5-methyl-furan-2-yl)-4-oxo-butyl ester (Table 8, entry 5). Prepared according to the general procedure from (*E*)-4-benzyloxy-but-2-enal (571 mg, 3.00 mmol), 2-methylfuran (90 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), trichloroacetic acid (7.7 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at −20 °C for 22 h to provide the title compound as a colorless oil (250.0 mg, 92% yield, 97% ee) after silica gel chromatography (5% EtAc / 5% DCM / hexanes). IR (film) 2950, 2897, 2828, 2730, 1721, 1602, 1567, 1451, 1385, 1315, 1272,

1219, 1176, 1118, 1070, 1026, 956.4, 942.4, 785.3, 711.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.71 (dd, *J* = 1.6, 3.0 Hz, 1H, CHO), 8.01- 7.95 (m, 2H, PhH), 7.56- 7.48 (m, 1H, PhH), 7.44- 7.35 (m, 2H, PhH), 6.02 (d, *J* = 3.0 Hz, 1H, ArH), 5.88- 5.83 (m, 1H, ArH), 4.54 (ddd, *J* = 1.4, 5.8, 11.0 Hz, 1H, OC**H**$_2$), 4.40 (ddd, *J* = 1.1, 6.9, 10.7 Hz, 1H, OC**H**$_2$), 3.78 (pentet, *J* = 6.6 Hz, 1H, C**H**$(CH_2)_2$), 2.95- 2.77 (m, 2H, C**H**$_2$CHO), 2.21 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) □ 200.3, 166.3, 151.6, 151.5, 133.3, 130.0, 129.8, 128.6, 107.4, 106.4, 66.3, 44.7, 33.4, 13.9; $[□]_D$ = –3.2 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using Chiralcel OD-H column (1.6 x 25 cm) and OD-H guard (1.6 x 5 cm) (3.0% ethanol / hexanes, 1 mL/mn); *S* isomer t_r = 102.6 min and *R* isomer t_r = 91.8 min.

(*R*)-2-(5-Methyl-furan-2-yl)-4-oxo-butyric acid methyl ester (Table 8, entry 6). Prepared according to the general procedure from (*E*)-methyl-4-oxo-butenoate (342 μL, 3.00 mmol), 2-methylfuran (90 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), trichloroacetic acid (7.7 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at □30 °C for 16 h to provide the title compound as a colorless oil (166.0 mg, 85% yield, 95% ee) after silica gel chromatography (10% Et_2O / petroleum ether). IR (film) 2954, 2915, 2838, 2723, 1740, 1724, 1612, 1563, 1437, 1385, 1328, 1272, 1232, 1218, 1167, 1088, 1046, 1022, 979.3, 942.3, 788.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.71 (s, 1H, CHO), 6.00 (d, *J* = 3.0 Hz, 1H, ArH), 5.86- 5.82 (m, 1H, ArH), 4.16 (dd, *J* = 5.2, 9.1 Hz, 1H, $CHCO_2$), 3.66 (s, 1H, OCH_3), 3.25 (dd, *J* = 9.1, 18.7 Hz, 1H, C**H**$_2$), 2.84 (dd, *J* = 5.2, 18.7 Hz, 1H, C**H**$_2$), 2.19 (s, 3H, $ArCH_3$); ^{13}C NMR (75

MHz, $CDCl_3$) δ 199.2, 171.4, 152.1, 148.5, 108.1, 106.6, 52.9, 44.6, 39.1, 13.8; HRMS (CI) exact mass calcd ($C_9H_{12}O_3$) requires *m/z* 196.0736, found *m/z* 196.0731. $[\alpha]_D$ = –80.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (80 °C isotherm, 1 mL/min); *S* isomer t_r = 104.0 min and *R* isomer t_r = 103.5 min.

(*R*)-2-Furan-2-yl-oxo-butyric acid ethyl ester (Table 9, entry 1). Prepared according to the general procedure from (*E*)-ethyl-4-oxo-butenoate (128 mg, 1.00 mmol), furan (909 μL, 12.5.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), and trichloroacetic acid (7.7 μL, 0.10 mmol) at −40 °C for 8 h to provide the title compound as a colorless oil (152.5 mg, 78% yield, 93% ee) after silica gel chromatography (10% EtAc / hexanes). IR (film) 3121, 2984, 2834, 2729, 1735, 1725, 1590, 1505, 1388, 1370, 1325, 1269, 1230, 1181, 1164, 1095, 1043, 1012, 933.0, 740.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H, CHO), 7.31 (dd, *J* = 0.8, 1.6 Hz, 1H, ArH), 6.28 (dd, *J* = 1.9, 3.2 Hz, 1H, ArH), 6.16 (d, *J* = 3.3 Hz, 1H, ArH), 4.23 (dd, *J* = 4.9, 9.1 Hz, 1H, $CHCO_2$), 4.14 (m, 2H, CH_2Me), 3.28 (ddd, *J* = 0.8, 9.1, 18.7 Hz, 1H, C**H**$_2$CHO), 2.89 (ddd, *J* = 0.6, 5.2, 18.4 Hz, 1H, C**H**$_2$CHO), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 170.7, 150.6, 142.4, 110.7, 107.3, 61.9, 44.5, 39.3, 14.4; HRMS (CI) exact mass calcd ($C_9H_{12}O_3$) requires *m/z* 196.0736, found *m/z* 196.0741. $[\alpha]_D$ = –56.4 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (100 °C isotherm, 1 mL/min); *S* isomer t_r = 55.4 min and *R* isomer t_r = 49.7 min.

(*R*)-3-(4,5-dimethyl-furan-2-yl)-butyraldehyde (Table 9, entry 3). Prepared according to the general procedure from (*E*)-crotonaldehyde (250 μL, 3.00 mmol), 2,3-dimethylfuran (106 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), cyanoacetic acid (8.5 mg, 0.10 mmol), and $CHCl_3$ (2.00 mL) at −40 °C for 41 h to provide the title compound as a colorless oil (123.8 mg, 74% yield, 98% ee) after silica gel chromatography (10% Et_2O / petroleum ether). IR (film) 2968, 2926, 2884, 2823, 2729, 1726, 1566, 1218, 1021, 782.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.2 Hz, 1H, CHO), 5.77 (s, 1H, ArH), 3.39- 3.25 (m, 1H, CHMe), 2.74 (ddd, *J* = 2.2, 6.9, 16.8 Hz, 1H, C**H**$_2$), 2.52 (ddd, *J* = 1.9, 5.8, 16.8 Hz, 1H, C**H**$_2$), 2.14 (s, 3H, $ArCH_3$), 1.88 (s, 3H, $ArCH_3$), 1.27 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 155.3, 146.0, 114.4, 107.6, 49.6, 28.2, 19.5, 11.6, 10.2; HRMS (CI) exact mass calcd for (M-1) ($C_9H_{12}O_3$) requires *m/z* 166.0994, found *m/z* 166.0989. $[\alpha]_D$ = −2.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (85 °C isotherm, 1 mL/min); *S* isomer t_r = 27.1 min and *R* isomer t_r = 28.6 min.

(*R*)-3-(5-Methoxy-furan-2-yl)-butyraldehyde (Table 9, entry 4). Prepared according to the general procedure from (*E*)-crotonaldehyde (250 μL, 3.00 mmol), 2-methoxyfuran (92 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), dichloroacetic acid (8.2 μL, 0.10 mmol), and $CHCl_3$ (4.00 mL) at −40 °C for 5 h to provide the title compound as a colorless oil (131.3 mg, 78% yield, 95% ee) after silica gel chromatography (10% Et_2O / petroleum ether). IR (film) 2973, 2937, 2837, 2726, 1725, 1617, 1589, 1458, 1438, 1385, 1341, 1261,

1227, 1177, 1054, 1017, 966.2, 942.4, 819.4, 744.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 2.2 Hz, 1H, CHO), 5.85 (dd, *J* = 2.8, 3.3 Hz, 1H, ArH), 4.99 (d, *J* = 3.0 Hz, 1H, ArH), 3.79 (s, 3H, OCH_3), 3.30 (sextet, *J* = 0.8, 1H, C**H**CH_3), 2.74 (ddd, *J* = 2.2, 6.6, 17.0 Hz, 1H, C**H**$_2$), 2.52 (ddd, *J* = 2.2, 7.1, 17.0 Hz, 1H, C**H**$_2$), 1.25 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 160.8, 148.0, 105.4, 79.5, 57.9, 49.3, 28.1, 19.2; HRMS (CI) exact mass calcd for ($C_9H_{12}O_3$) requires *m/z* 168.0786, found *m/z* 168.0792. $[\alpha]_D$ = −1.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (80 °C isotherm, 1 mL/min); *S* isomer t_r = 79.3 min and *R* isomer t_r = 80.8 min.

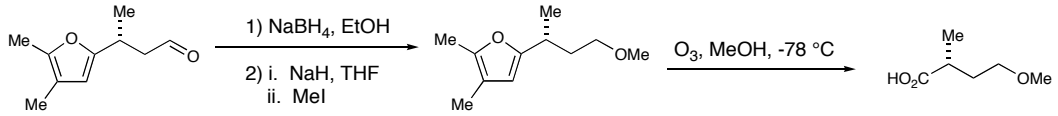
(*R*)-3-(5-Methoxy-thiophen-2-yl)-butyraldehyde (Table 9, entry 5). Prepared according to the general procedure from (*E*)-crotonaldehyde (250 μL, 3.00 mmol), 2-methoxythiophene (101 μL, 1.00 mmol), (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), trifluoroacetic acid (7.7 μL, 0.10 mmol), and $CHCl_3$ (2.00 mL) at −30 °C for 23 h to provide the title compound as a colorless oil (159.6 mg, 87% yield, 92% ee) after silica gel chromatography (10% Et_2O / petroleum ether). IR (film) 2963, 2927, 2830, 2724, 1724, 1561, 1510, 1453, 1433, 1408, 1378, 1238, 1206, 1176, 1149, 1106, 1081, 1052, 1025, 995.9, 772.4, 743.8, 715.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.9 Hz, 1H, CHO), 6.40 (dd, *J* = 0.8, 3.8 Hz, 1H, ArH), 5.95 (d, *J* = 3.8 Hz, 1H, ArH), 3.82 (s, 3H, OCH_3), 3.30 (sextet, *J* = 7.0, 1H, C**H**CH_3), 2.72 (ddd, *J* = 1.9, 6.9, 16.8 Hz, 1H, C**H**$_2$), 1.92 (ddd, *J* = 1.9, 7.1, 16.8 Hz, 1H, C**H**$_2$), 1.32 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 164.4, 135.5, 120.3, 102.9, 60.4, 52.3, 30.5, 23.0; HRMS (CI) exact mass calcd for ($C_9H_{12}O_2S$)

requires *m/z* 184.0558, found *m/z* 184.0560. $[\alpha]_D$ = −13.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (90 °C isotherm, 1 mL/min); *S* isomer t_r = 139.5 min and *R* isomer t_r = 145.8 min.

(*S*)-(*tert*-butyldimethylsilanyloxy)-2-phenyl-butyric acid methyl ester (13). (*S*)-3-(5-Methoxy-furan-2-yl)-3-phenyl-propionaldehyde (731 mg, 3.17 mmol) was added to a suspension of sodium borohydride (120 mg, 3.17 mmol) in ethanol (5 mL) at 0 °C. (*S*)-3-(5-Methoxy-furan-2-yl)-3-phenyl-propionaldehyde was judged to have been consumed by TLC after fifteen minutes at which time a solution of saturated $NaHCO_3$ (10 mL) was added and stirred until gas evolution ceased. The resulting solution was extracted with DCM (3x20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. To this crude oil was added CH_2Cl_2 (10 mL), imidazole (433 mg, 6.36 mmol) and *tert*-butyldimethylsilyl chloride (575 mg, 3.82 mmol). The reaction was stirred for 10 h then saturated aqueous NH_4Cl was added and the organics were extracted with CH_2Cl_2 (3x20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography to provide *tert*-butyl-[(*S*)-3-(5-methoxy-furan-2-yl)-3-phenyl-propoxy]-dimethyl-silane (**12**) (910 mg, 83% yield). IR (film) 3063, 3028, 2954, 2930, 2885, 2857, 1734, 1717, 1700, 1616, 1586, 1472, 1464, 1456, 1436, 1376, 1361, 1261, 1103, 1015, 940.9, 834.4, 776.1, 734.7, 699.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H, C_6H_5), 5.91 (dd, *J* = 0.8, 3.2 Hz, 1H, ArH), 5.02 (d, *J* = 3.2 Hz, 1H, ArH), 4.05 (t, *J* = 7.7 Hz, 1H, CHPh), 3.78 (s, 3H, OCH_3), 3.63-3.46 (m, 2H, CH_2O), 2.33-2.20 (m, 1H, C**H**$_2$$CH_2O$), 2.07-1.95 (m, 1H, C**H**$_2$$CH_2O$), 0.89 (s, 9H, $C(CH_3)_3$), 0.00 (s, 3H, $SiCH_3$), 0.00 (s, 3H,

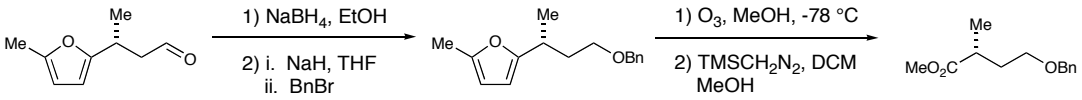
$SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 160.7, 147.5, 142.5, 128.3, 127.9, 126.4, 106.2, 79.3, 60.5, 57.5, 41.0 37.3, 25.9, 18.2, –5.40, –5.41; HRMS (CI) exact mass calcd for ($C_9H_{12}O_2S$) requires *m*/*z* 346.1964, found *m*/*z* 346.1971. Ozone was bubbled through a solution of methanol at –78 °C containing *tert*-butyl-[(*S*)-3-(5-methoxy-furan-2-yl)-3-phenyl-propoxy]-dimethyl-silane (**12**) (100 mg, 0.29 mmol) until the reaction turned a yellowish green. Nitrogen was then bubbled through the solution for an additional 20 min and the reaction was then allowed to warm to room temperature overnight and concentrated. The resulting oil was dissolved in DCM (1.5 mL) and MeOH (150 μL) to which TMS-diazomethane was added dropwise until a yellow color persisted. The residual TMS-diazomethane was quenched by the dropwise addition of acetic acid until the yellow color disappeared. The reaction was then treated with an excess of saturated aqueous $NaHCO_3$, extracted with EtOAc (3 x 20ml), dried over $MgSO_4$ and purified by silica gel chromatography to provide the title compound **13** (73 mg, 83% yield, 94% ee). IR (film) 3031, 2954, 2929, 2895, 2857, 1737, 1602, 1494, 1472, 1435, 1388, 1361, 1317, 1257, 1231, 1194, 1163, 1105, 1066, 1006, 950.3, 834.7, 776.1, 734.9, 698.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.33-7.23 (m, 5H, C_6H_5), 3.82 (t, *J* = 7.7 Hz, 1H, CHPh), 3.65 (s, 3H, OCH_3), 3.62-3.55 (m, 1H, C**H**$_2$O), 3.54-3.45 (m, 1H, C**H**$_2$O), 2.38-2.25 (m, 1H, C**H**$_2$$CH_2O$), 2.00-1.87 (m, 1H, C**H**$_2$$CH_2O$), 0.89 (s, 9H, $C(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 174.5, 138.9, 142.5, 128.6, 128.1, 127.2, 60.3, 51.9, 47.6, 36.2, 25.9, 18.3, –5.46, –5.50; HRMS (CI) exact mass calcd for ($C_9H_{12}O_2S$) requires *m*/*z* 382.2257, found *m*/*z* 382.2257. The enantiomeric ratio was determined by GLC using a Bodman Chiraldex □-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); *S* isomer t_r = 610.0 min and *R* isomer t_r = 617.8 min.

Stereochemical Analysis



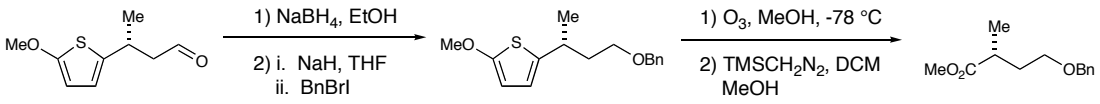
Determination of the absolute stereochemistry of (*R*)-3-(4,5-dimethyl-furan-2-yl)-butyraldehyde by correlation to (*S*)-4-methoxy-2-methyl-butyric acid.[14] (*R*)-3-(4,5-dimethyl-furan-2-yl)-butyraldehyde (650 mg, 3.91 mmol) was added to a suspension of sodium borohydride (148 mg, 3.91 mmol) in ethanol (10 mL) at 0 °C. (*R*)-3-(4,5-dimethyl-furan-2-yl)-butyraldehyde was judged to have been consumed by TLC after fifteen minutes and the reaction was quenched by the addition of a solution of saturated $NaHCO_3$ until gas evolution ceased. The resulting solution was extracted with DCM (3x20mL), dried over $MgSO_4$, and concentrated *in vacuo* to give (*R*)-3-(4,5-dimethyl-furan-2-yl)-butan-1-ol (520 mg, 3.13 mmol). (*R*)-3-(4,5-dimethyl-furan-2-yl)-butan-1-ol (400 mg, 2.40 mmol) was added to a suspension of sodium hydride (114 mg, 4.6 mmol) in THF (6 mL) and stirred at room temperature for 30 min. Iodomethane (448 μL, 7.20 mmol) was added slowly and allowed to stir for 10 h. The reaction was then quenched with water and extracted with DCM (3x20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography in 2% EtOAc / hexanes to provide (*R*)-5-(3-methoxy-1-methyl-propyl)-2,3-dimethyl-furan (310 mg, 1.70 mmol). Ozone was bubbled through a solution of methanol at –78 °C containing (*R*)-5-(3-methoxy-1-methyl-propyl)-2,3-dimethyl-furan (310 mg, 1.70 mmol) until the reaction turned a yellowish green. Oxygen was then bubbled through the solution for an additional 20 min and the reaction was then warmed to room temperature and concentrated. To the resulting oil,

1 N NaOH (20 mL) was added and the solution was subsequently extracted with diethyl ether (2x30 mL). The aqueous phase was then acidified with 1 N HCl and extracted with DCM (3x20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography in 20% EtOAc / hexanes to provide (*R*)-4-methoxy-2-methyl-butyric acid (64 mg, 0.48 mmol). $[\alpha]_D = -17.6$ (c = 1.0, Et_2O); reported rotation for (*S*)-4-methoxy-2-methyl-butyric acid $[\alpha]_D = +12.2$ (c = 15.28, Et_2O).



Determination of the absolute stereochemistry of (*R*)-3-(5-Methyl-furan-2-yl)-butyraldehyde by correlation to (*S*)-4-benzyloxy-2-methyl-butyric acid methyl ester.[14] (*R*)-3-(5-Methyl-furan-2-yl)-butyraldehyde (1.54 g, 10.0 mmol) was added to a suspension of sodium borohydride (189 mg, 5.00 mmol) in ethanol (15 mL) cooled to 0 °C. (*R*)-3-(5-Methyl-furan-2-yl)-butyraldehyde was judged to have been consumed by TLC after fifteen minutes and the reaction was quenched by the addition of a solution of saturated $NaHCO_3$ until gas evolution ceased. The resulting solution was extracted with DCM (3x20mL), dried over $MgSO_4$, and concentrated *in vacuo* to give (*R*)-3-(5-methyl-furan-2-yl)-butan-1-ol (1.39 g, 9.03 mmol). (*R*)-3-(4,5-dimethyl-furan-2-yl)-butan-1-ol (500 mg, 3.20 mmol) was added to a suspension of sodium hydride (153 mg, 6.40 mmol) in THF (6 mL) and stirred at room temperature for 30 min. Benzylbromide (1.43 mL, 9.60 mmol) was added slowly and allowed to stir for 10 h. The reaction was then quenched with water and extracted with DCM (3x20 mL), dried over magnesium sulfate,

concentrated *in vacuo* and purified by silica gel chromatography in 2% EtOAc / hexanes to provide (*R*)-2-(3-benyloxy-1-methyl-propyl)-5-methyl-furan (420 mg, 1.72 mmol). Ozone was bubbled through a solution of methanol at –78 °C (*R*)-2-(3-benyloxy-1-methyl-propyl)-5-methyl-furan (300 mg, 1.23 mmol) until the reaction turned a yellowish green. Oxygen was then bubbled through the solution for an additional 20 min and the reaction was then warmed to room temperature and concentrated. To the resulting oil, 1 N NaOH (20 mL) was added and the solution was subsequently extracted with diethyl ether (2x30 mL). The aqueous phase was then acidified with 1 N HCl and extracted with DCM (3x20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to provide (*S*)-4-benzyloxy-2-methyl-butyric acid (120 mg, 0.57 mmol). TMS-diazomethane was added dropwise to a solution of the (*S*)-4-benzyloxy-2-methyl-butyric acid (69 mg, 0.33 mmol) in DCM (1.5 mL) and MeOH (150 μL) until a yellow color persisted. The residual TMS-diazomethane was quenched by the dropwise addition of acetic acid until the yellow color disappeared. The reaction was then treated with an excess of saturated aqueous sodium bicarbonate, extracted with EtOAc (3 x 20ml), dried over $MgSO_4$ and purified by silica gel chromatography in 20% EtOAc / hexanes to provide (*R*)-4-benzyloxy-2-methyl-butyric acid methyl ester (40 mg, 0.18 mmol). $[\alpha]_D$ = –22.9 (c = 1.0, $CHCl_3$); reported rotation for (*R*)-4-benzyloxy-2-methyl-butyric acid methyl ester $[\alpha]_D$ = +24.9 (c = 9.5, $CHCl_3$).



Determination of the absolute stereochemistry of (*R*)-3-(5-Methoxy-thiophen-2-yl)-butyraldehyde by correlation to (*S*)-4-benzyloxy-2-methyl-butyric acid methyl ester.[14] (*R*)-3-(5-Methyl-thiophen-2-yl)-butyraldehyde (0.65 g, 3.5 mmol) was added to a suspension of sodium borohydride (120 mg, 3.2 mmol) in ethanol (10 mL) cooled to 0 °C. (*R*)-3-(5-Methyl-thiophen-2-yl)-butyraldehyde was judged to have been consumed by TLC after fifteen minutes and the reaction was quenched by the addition of a solution of saturated $NaHCO_3$ until gas evolution ceased. The resulting solution was extracted with DCM (3x20mL), dried over $MgSO_4$, and concentrated *in vacuo* to give (*R*)-3-(5-methyl-thiophen-2-yl)-butan-1-ol (0.60 g, 3.2 mmol). (*R*)-3-(5-methyl-thiophen-2-yl)-butan-1-ol (0.60 g, 3.2 mmol) was added to a suspension of sodium hydride (154 mg, 6.40 mmol) in THF (6 mL) and stirred at room temperature for 30 min. Benzylbromide (1.43 mL, 9.60 mmol) was added slowly and allowed to stir for 10 h. The reaction was then quenched with water and extracted with DCM (3x20 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography in 2% EtOAc / hexanes to provide (*R*)-2-(3-benyloxy-1-methyl-propyl)-5-methyl-thiophene (705 mg, 2.55 mmol). Ozone was bubbled through a solution of methanol at –78 °C (*R*)-2-(3-benyloxy-1-methyl-propyl)-5-methyl-thiophene (300 mg, 1.09 mmol) until the reaction turned a yellowish green. Oxygen was then bubbled through the solution for an additional 20 min and the reaction was then warmed to room temperature and concentrated. To the resulting oil, 1 N NaOH (20 mL) was added and the solution was subsequently extracted with diethyl ether (2x30 mL). The aqueous phase was then acidified with 1 N HCl and extracted with DCM (3x20 mL), dried over magnesium sulfate, and concentrated *in vacuo* to provide (*S*)-4-benzyloxy-2-methyl-butyric acid (20 mg, 0.096 mmol). TMS-

diazomethane was added dropwise to a solution of the (*S*)-4-benzyloxy-2-methyl-butyric acid (20 mg, 0.096 mmol) in DCM (1.5 mL) and MeOH (150 μL) until a yellow color persisted. The residual TMS-diazomethane was quenched by the dropwise addition of acetic acid until the yellow color disappeared. The reaction was then treated with an excess of saturated aqueous sodium bicarbonate, extracted with EtOAc (3 x 20ml), dried over $MgSO_4$ and purified by silica gel chromatography in 20% EtOAc / hexanes to provide (*R*)-4-benzyloxy-2-methyl-butyric acid methyl ester (10 mg, 0.045 mmol). $[\alpha]_D$ = −19.0 (c = 1.0, $CHCl_3$); reported rotation for (*R*)-4-benzyloxy-2-methyl-butyric acid methyl ester $[\alpha]_D$ = +24.9 (c = 9.5, $CHCl_3$).

V. References

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Chapter 3

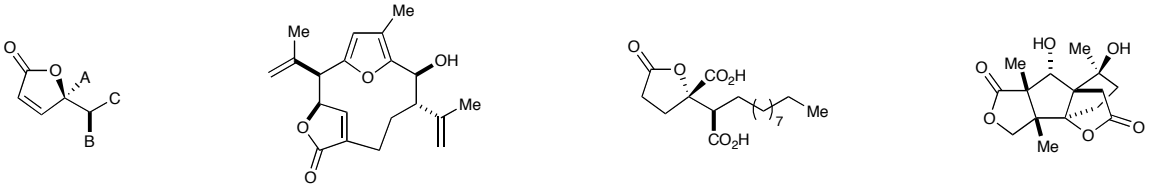
Enantioselective Organocatalytic Mukaiyama-Michael Reaction

I. Introduction

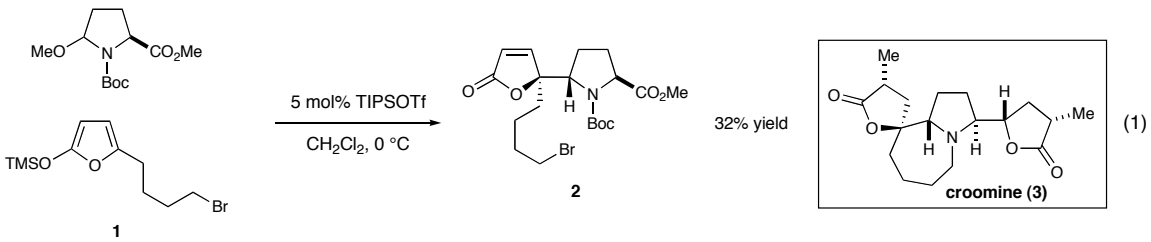
The γ-Butenolide Architecture

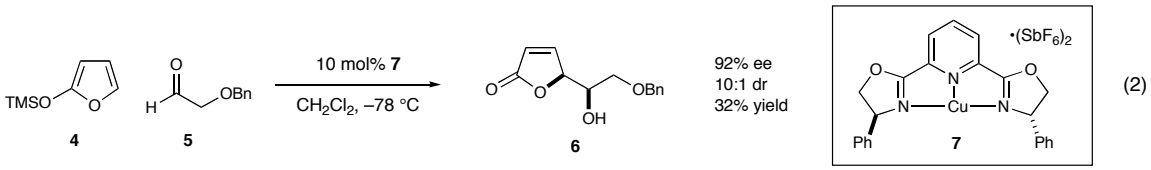
The γ-butenolide architecture is represented in over 13,000 natural products[1] (Figure 1) and contains functional handles that can be utilized for further chemical elaboration. For these reasons, it has become an important platform for the development of new stereoselective methodologies. A variety of diastereoselective methods have been developed for stereoselective construction of γ-butenolide architecture. Martin's group has utilized a functionalized silyloxyfuran **1** to undergo a vinylogous Mannich reaction to generate the γ-butenolide functionality **2** in their synthesis of (+)-croomine (**3**) (eq 1).[2,3] Enantioselective methodology has been developed by the Evans group, which utilizes chiral Lewis acid catalyzed reaction of silyloxyfuran **4** with (benzyloxy)acetaldehyde (**5**) to produce the enantioenriched γ-butenolides **6** (eq 2).[4,5]

Scheme 1. Butenolide containing natural products



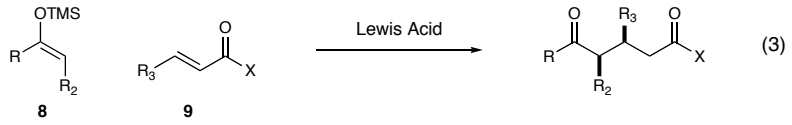
γ-butenolide | kallolide | spiculisporic acid | merrilactone B





The Mukaiyama-Michael Reaction

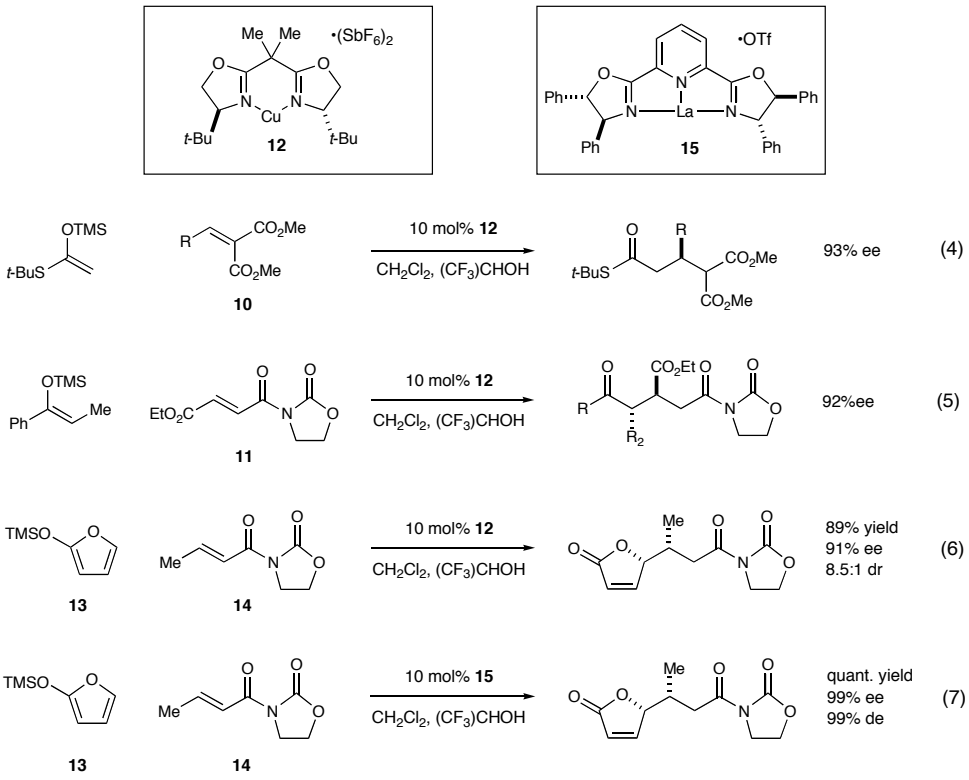
Since its discovery by Mukaiyama in 1974,[6] the Mukaiyama-Michael reaction has become a powerful reaction for stereoselective carbon–carbon bond formation. This addition of silyl enol ethers **8** to □,□-unsaturated carbonyl compounds **9** is a proven method for stereoselective construction in an acyclic framework (eq 3). The use of silyl enol ethers for additions to □,□-unsaturated carbonyls provides mild reaction conditions increasing the functional group tolerance these Michael additions.



Enantioselective Catalytic Mukaiyama-Michael Reaction

To date, there remain relatively few methods to carry out catalytic enantioselective Mukaiyama-Michael reactions and these are limited to very specific systems. The Evans group developed a copper(II) bis(oxazoline) **12** catalyzed enantioselective Mukaiyama-Michael reaction with alkylidene malonates **10** (eq 4)[7] or unsaturated acyl oxazolidinones **11** (eq 5)[8] as Michael acceptors. The groups of

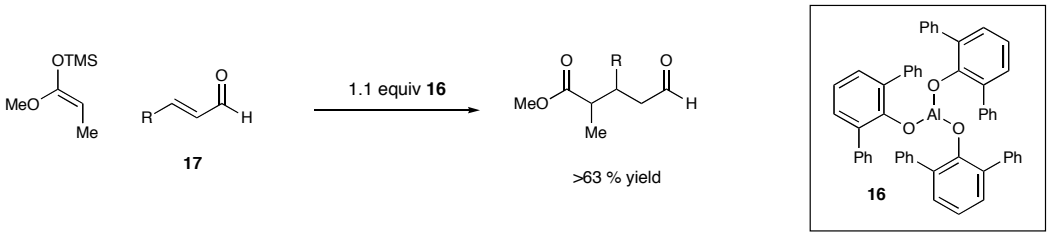
Katsuki[9,10] and Desimoni[11] utilized silyloxyfuran **13** and acyl oxazolidinones **14**, but differ over the choice of chiral Lewis acid (eq **6**, **7**). These two technologies represented the state of the art for the construction of the γ-butenolide architecture using an asymmetric Mukaiyama-Michael strategy, though both of these processes were limited by the need of a bidentate chelating substrate and long reaction times.



Mukaiyama-Michael vs. Mukaiyama-Aldol

The exposure of a latent enolate equivalent to an α,β-unsaturated aldehyde in the presence of a Lewis acid presents a regioselectivity issue betweeen 1,2-addition (aldol) and 1,4-addition manifold (Mukaiyama-Michael). It is commonly accepted that α,β-unsaturated aldehydes react with enol silanes through the 1,2-addition pathway. In fact, the only example of a 1,4-addition comes from the Yamamoto group who utilized

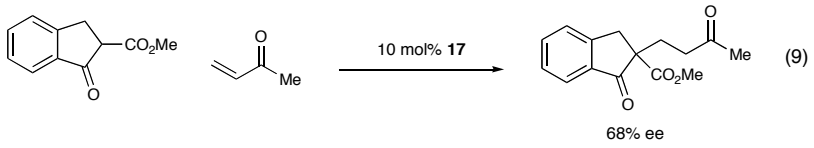
aluminum Lewis acid **16** to activate the π-system of the α,β-unsaturated aldehyde **17**. The sterically bulky ligands of the Lewis acid **16** shield the aldehyde from 1,2-addition, resulting in reaction through the unprecedented 1,4-addition manifold (eq 8).[12]



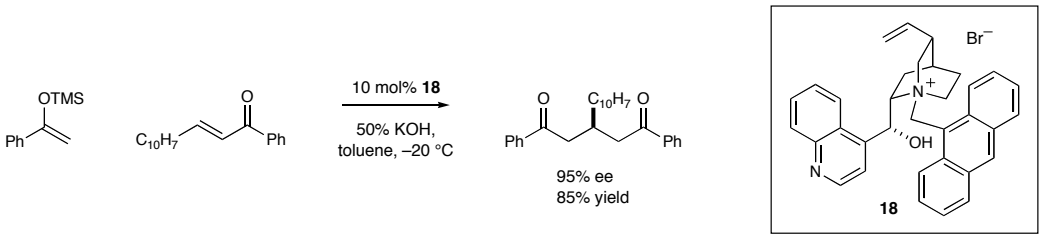
(8)

Organocatalysis of the Michael Reaction

Several organocatalytic approaches to the enantioselective Michael reaction have been reported since 1975 when quinine was used to catalyze the conjugate addition of 1,3-dicarbonyls (eq 9).[13] More recently, Corey's group used chiral quaternary ammonium salts of cinchona alkaloid derivatives to catalyze the 1,4-addition of silyl enol ethers to α,β-unsaturated ketones (eq 10).[14,15]



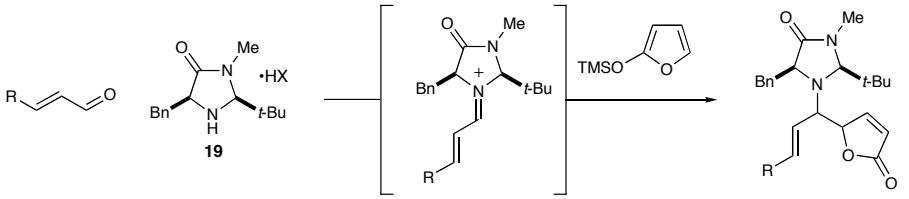
(9)



(10)

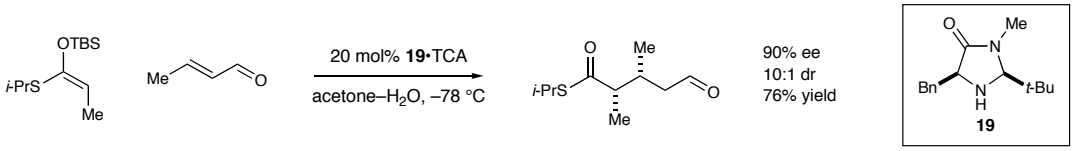
Iminium Catalyzed Michael Reactions

The previous chapter described the conjugate addition of furan nucleophiles to α,β-unsaturated aldehydes. Even with this precedent, it was unknown whether silylketene acetals would undergo 1,4-addition because of the large amount of literature to the contrary. Addition by way of a 1,4-addition manifold was not only desired because it would provide a previously inaccessible reactivity pattern, but it was also necessary to achieve catalyst turnover; 1,2-Addition of a nucleophile permanently incorporates the imidazolidinone catalyst preventing a catalytic process (eq 11).



(11)

Previous work in our group by Christopher Borths provided the first imidazolidinone catalyzed 1,4-addition of silylketene acetals to α,β-unsaturated aldehydes. This work paved the way for a variety of Mukaiyama-Michael reactions to access a diverse range of asymmetric architectures (eq 12).[16]



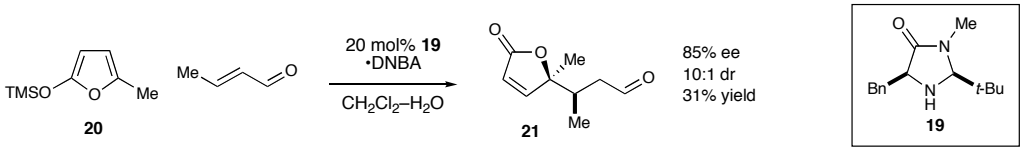
(12)

II. Results and Discussion

Organocatalytic Access to the γ-Butenolide Architecture

Our enantioselective organocatalytic butenolide synthesis was first examined using silyloxy furan **20**, imidazolidinone catalyst **19** and crotonaldehyde (eq 13).

Preliminary studies revealed that the proposed conjugate addition was indeed possible with excellent levels of *syn* diastereoselectivity and enantiocontrol (eq 13, 10:1 *anti*:*syn*, 85% ee), however, catalytic efficiency was poor (31% yield).



(3)

Catalyst substrate complexes arising from 1,2-addition of the silyloxyfuran were not observed. With this in mind, we made the assumption that imidazolidinone turnover was being inhibited by loss of H_2O from the catalytic cycle (presumably via formation of $(TMS)_2O$). We therefore examined the use of protic additives that might competitively scavenge the putative silyl cation intermediate (Scheme 1). While a variety of alkyl alcohol additives were found to be productive in this context (Table 1, entries 2–5), the addition of excess H_2O (2 equivs) provided optimal reaction efficiency (entries 5 and 6, ≥84% yield) and stereoselectivities at –70 °C (entry 6, *syn*:*anti* 22:1, 92% ee).

Scheme 2. Catalytic cycle of the organocatalyzed Mukaiyama-Michael reaction

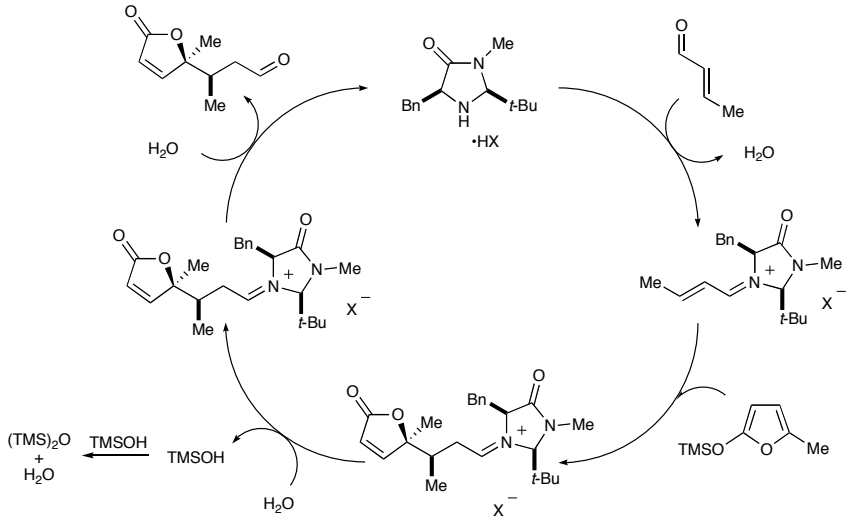
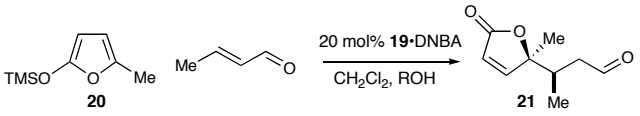


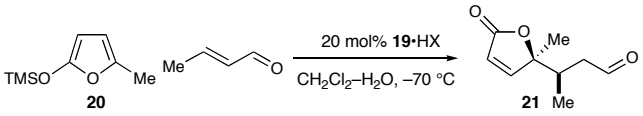
Table 1. The effect of protect nucleophiles on the organocatalyzed Mukaiyama-Michael



entry	ROH	temp (°C)	time (h)	% yield	*syn*:*anti*	% ee
1	--	–40	10	31	10:1	85
2	*i*-PrOH	–40	10	83	16:1	84
3	$(CF_3)_2CHOH$	–40	10	42	10:1	83
4	phenol	–40	10	58	11:1	82
5	H_2O	–40	10	93	16:1	85
6	H_2O	–70	11	84	22:1	92

A variety of acid cocatalysts with pK_a between 0.5 and 2.5 provide good levels of reaction rate and high levels of enantioselectivity (Table 2). Optimum asymmetric induction and efficiency was exhibited by the amine salt **19**•2,4-dinitrobenzoic acid (DBNA) in CH_2Cl_2–H_2O to afford the stereochemically enriched butenolide **21** in 92% ee (entry 4), prompting us to select these catalytic conditions for further exploration.

Table 2. The effect of acid cocatalyst on the organocatalyzed Mukaiyama-Michael

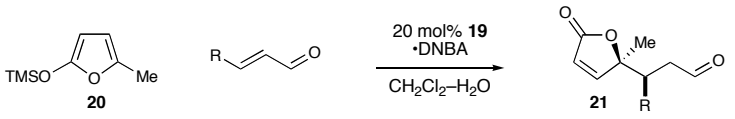


entry	HX	pK_a	% conversion	dr	% ee
1	MCA	2.87	10	35:1	87
2	CNAcOH	2.47	55	36:1	88
3	2-nitrobenzoic	2.21	13	31:1	90
4	2,4-nitrobenzoic	1.85	53	36:1	92
5	DBA	1.48	36	32:1	90
6	DCA	1.35	54	33:1	90
7	DFA	1.34	20	32:1	89
8	TBA	0.72	55	27:1	88
9	TFA	0.52	58	28:1	85
10	TCA	0.51	48	27:1	84

Experiments that probe the scope of the □,□-unsaturated aldehyde component are summarized in Table 3. There appears to be significant latitude in the steric demands of

the β-olefin substituent (entries 1–4, R = Me, Pr, *i*-Pr, Ph) that permit access to a broad variety of 5-(1-alkyl)-5-methyl-furanones (*syn*:*anti* 7:1 to 31:1, 84–99% ee). Moreover, variation in the electronic nature of the aldehyde component has little influence on the relative or absolute sense of stereoinduction. For example, high levels of asymmetric induction are available with enals that do not readily participate in iminium ion formation (entry 6, R = CO_2Me, 84% yield, 99% ee), as well as aldehydes that provide stable iminium intermediates (entry 7, R = Ph, 77% yield, 99% ee). In accordance with our mechanistic postulate, it is important to note that products arising from 1,2-iminium addition were never observed with any of the aldehydes examined.

Table 3. Organocatalyzed Mukaiyama-Michael: aldehyde substrate scope

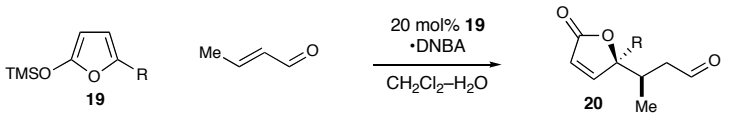


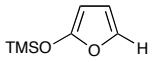
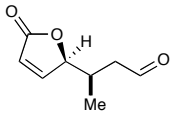
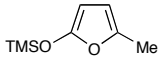
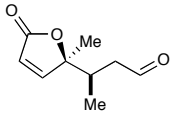
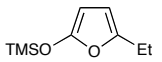
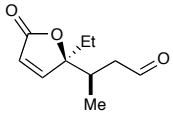
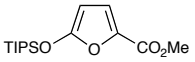
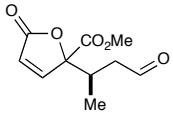
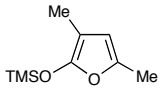
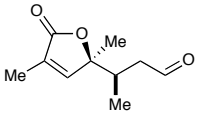
entry	R	temp (°C)	time (h)	% yield	*syn*:*anti*	% ee
1	Me	–70	11	81	22:1	92
2	Pr	–50	20	87	31:1	84
3	*i*-Pr	–20	30	80	7:1	98
4	Ph	–40	30	77	1:6	99
5	CH_2OBz	–70	24	86	20:1	90
6	CO_2Me	–60	22	84	11:1	99

Significant structural variation in the silyloxy furan system can also be realized (Table 4). Importantly, the reaction appears quite tolerant with respect to the substituent at the furanyl 5-position (entries 1-4, R = H, Me, Et, CO_2Me 90–92% ee). While high levels of *syn*-5,5'-stereogenicity is available in the construction of a wide variety of β butenolide systems (entries 1–4, 6), the corresponding *anti*-isomer can also be forged with excellent levels of stereoselectivity via the appropriate selection of co-catalyst and solvent (entry 5, *syn*:*anti* 1:7, 98% ee, 83% yield). Moreover, the introduction of alkyl

substituents at C(3) on the furan ring can also be accommodated without loss in diastereocontrol or enantioinduction (entry 6, *syn:anti* 24:1, 98% ee).

Table 4. Organocatalyzed Mukaiyama-Michael: silyloxy furan substrate scope



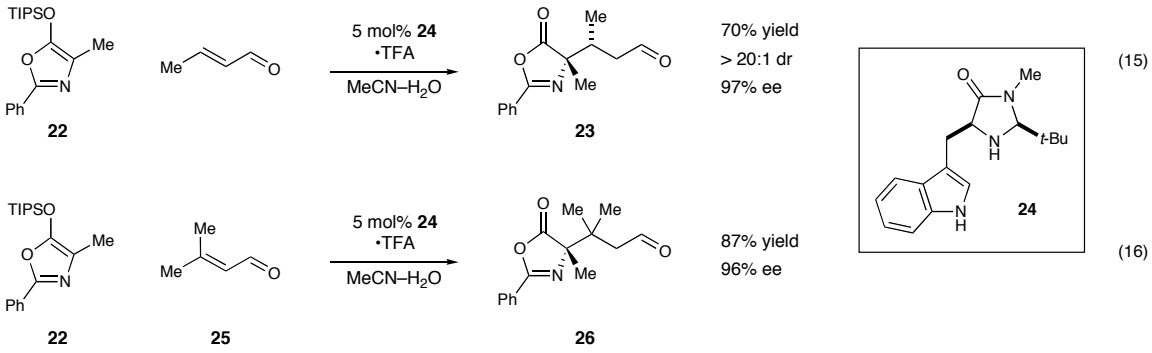
entry	siloxy furan	product	% yield	*syn:anti*	% ee
1			87	8:1	90
2			80	22:1	92
3			83	16:1	90
4			86	6:1	98[a]
5			83	1:7	98[b]
6			73	24:1	90

[a] With 20 mol% catalyst **1**•TFA in THF. [b] With 20 mol% catalyst **1**•TfOH in $CHCl_3$.

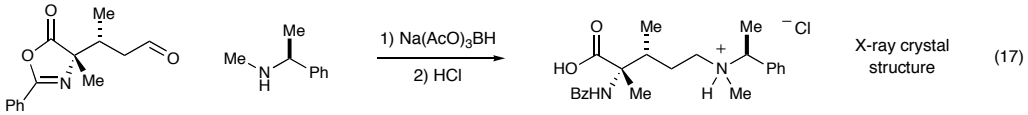
Organocatalytic Access to β-amino acids

The increasing importance of non-natural amino acids for drug design and academic endeavors has inspired a multitude of synthetic methodologies for their construction. However, many of these methods are limited by their inability to access geminally disubstituted β-amino acids. Following the discovery of the Mukaiyama–Michael reaction of silyloxy furans, we postulated that the analogous asymmetric

addition of silyloxy oxazoles to enals would provide a convenient route to α-amino acids bearing fully substituted β-stereocenters.



Preliminary results demonstrated that silyloxy oxazole **22** efficiently generates the cyclic protected α-amino acid **23** (eq 15). The vicinal stereocenters of **23** were produced as a single observable diastereomer in 97% ee. Interestingly, exposure of the β-facially degenerate enal **25** to silyloxy oxazole **22** provided the protected α-amino acid **26** in 96% ee (eq 16). Purification of **26** with pH neutral silica gel was necessary to achieve high levels of chemical yield. The relative and absolute stereochemistries of **23** were confirmed by conversion to the HCl salt **27** through reductive amination followed by acidification, which crystallized and was analyzed X-ray crystallography (eq 17).



After the results in equations 15 and 16, Catharine Larsen undertook the completion of this project, providing additional understanding of this process and a greatly expanded substrate scope.[17]

III. Conclusion

An enantioselective Mukaiyama–Michael reaction for the construction of the γ-butenolide architecture[18] and β-amino acids has been described. This work culminated in the first highly enantioselective Mukaiyama–Michael reaction utilizing α,β-unsaturated aldehydes, further demonstrating the broad utility of enantioselective iminium activation. This methodology has been further utilized by Nicole Goodwin to facilitate the enantioselective synthesis of spiculisporic acid and 5-*epi*-spiculisporic acid.[18]

IV. Experimental Section

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[19] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[20] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-DM or Γ-TA (30 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralcel AD column (1.6 x 25 cm) and AD guard (1.6 x 5 cm),

Chiralcel OD-H (1.6 x 25 cm) and OD guard (1.6 x 5 cm), or Chiralcel AS (1.6 x 25 cm) and AS guard (1.6 x 5 cm) as noted.

Procedures

Trimethyl-(5-ethyl-furan-2-yloxy)-silane. To a round bottom flask equipped with a magnetic stir bar and charged with CH_2Cl_2 (50 mL) was added 5-ethyl-5*H*-furan-2-one[21] (6.5 g, 58 mmol) and triethylamine (11 mL, 81 mmol), which was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (12 mL, 64 mmol) was added slowly and allowed to stir at room temperature for 6 hours. The reaction mixture was concentrated *in vacuo* and the top layer was decanted and purified by distillation (14 mmHg, 94 °C) to provide the title compound as a pale yellow oil (7.6 g, 71% yield).

(3,5-Dimethyl-furan-2-yloxy)-trimethyl-silane. To a round bottom flask equipped with a magnetic stir bar and charged with CH_2Cl_2 (5 mL) was added 3,5-dimethyl-3*H*-furan-2-one[22] (0.56 g, 5.0 mmol) and triethylamine (0.97 mL, 7.0 mmol), which was cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (0.99 mL, 5.5 mmol) was added slowly and allowed to stir at room temperature for 6 hours. The reaction mixture was concentrated *in vacuo* and the top layer was decanted and purified by distillation (40 mmHg, 85 °C) to provide the title compound as a colorless oil (0.62 g, 68% yield).

General Procedure: To a 2-dram vial equipped with a magnetic stir bar and charged with (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one was added

solvent, 2,4-dinitrobenzoic acid and aldehyde, then placed in a bath at the appropriate temperature. The solution was stirred for 10 min before the addition of the siloxy-furan substrate in one portion. The resulting solution was stirred at constant temperature until reaction was determined to be complete by GLC conversion assay using dibenzyl ether as an internal standard. The reaction mixture was then transferred cold through a silica gel plug with ether into a flask and carefully concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (solvents noted) and fractions carefully concentrated *in vacuo* to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

(*3R,2'R*)-3-(2'-Methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-butyraldehyde (Table 3, entry 1). Prepared according to the general procedure from (*E*)-crotonaldehyde (166 μL, 2.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at −70 °C for 11 h to provide the title compound as a colorless oil (135.5 mg, 81% yield, 22 : 1 dr, 92% ee) after silica gel chromatography (40% EtOAc/ hexanes). IR (film) 3082, 2968, 2729, 1752, 1721, 1379, 1249, 1119, 948.1, 818.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.38 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 6.09 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.66-2.52 (m, 2H, MeCH, C**H**$_2$), 1.97-1.82 (ddd, *J* = 2.2, 9.9, 18.7 Hz, 1H, C**H**$_2$), 1.47 (s, 3H, OCCH$_3$); 0.99 (d, *J* = 7.1 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 158.7, 121.8, 100.2, 90.7, 46.0, 35.0, 23.2, 16.2; HRMS (CI) exact mass calcd for ($C_9H_{12}O_3$) requires *m/z* 168.0786, found *m/z* 168.0781. $[\alpha]_D$ = +46 9 (c =

1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex -TA (30 m x 0.25 mm) column (100 °C isotherm for 7 min, then 160 °C isotherm , 1 mL/min); (*3S, 2'S*) isomer t_r = 22.8 min and (*3R, 2'R*) isomer t_r = 23.8 min.

(*3R,2'R*)-3-(2'-Methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-hexanal (Table 3, entry 2). Prepared according to the general procedure from (*E*)-hexenal (348 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at 50 °C for 20 h to provide the title compound as a colorless oil (170.0 mg, 87% yield, 31 : 1 dr, 84% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3093, 2960, 2863, 2722, 1757, 1722, 1602, 1455, 1380, 1286, 1247, 1198, 1119, 1094, 1034, 951.8, 821.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.57 (t, *J* = 1.6 Hz, 1H, CHO), 7.31 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 5.92 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.36-2.14 (m, 3H, C**H**C**H$_2$**CHO), 1.38-0.98 (m, 4H, C**H$_2$**C**H$_2$**), 1.32 (s, 3H, OCCH$_3$); 0.74 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) 200.8, 171.9, 159.4, 121.5, 91.0, 44.1, 30.0, 33.0, 23.2, 21.2, 14.3; HRMS (CI) exact mass calcd for ($C_{11}H_{16}O_3$) requires *m/z* 196.1100, found *m/z* 196.1093. $[]_D$ = +21.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex -TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3S, 2'S*) isomer t_r = 13.4 min and (*3R, 2'R*) isomer t_r = 14.7 min.

(*3S,2'R*)-4-Methyl-3-(2'-methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-pentanal (Table 2, entry 3). Prepared according to the general procedure from (*E*)-4-methyl-2-pentenal (350 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and toluene (4.0 mL) at −20 °C for 30 h to provide the title compound as a colorless oil (156.1 mg, 80% yield, 7 : 1 dr, 98% ee) after silica gel chromatography (40% EtOAc/ hexanes). IR (film) 3093, 2963, 2874, 2722, 1758, 1723, 1602, 1467, 1389, 1371, 1260, 1236, 1115, 1088, 1040, 953.0, 822.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (t, *J* = 1.6 Hz, 1H, CHO), 7.31 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 5.92 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.43 (ddd, *J* = 2.7, 6.0, 8.8 Hz, 1H, CHC**H**CH$_2$), 2.24 (dd, , *J* = 1.6, 6.0, 8.8 Hz, 2H, C**H$_2$**), 1.88-1.74 (m, 1H, C**H**(CH$_3$)$_2$), 1.30 (s, 3H, OCCH$_3$); 0.78 (s, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)$_2$); 0.64 (s, *J* = 7.1 Hz, 3H, CH(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.9, 159.8, 121.3, 91.8, 44.7, 39.5, 28.1, 24.5, 23.3, 17.9; HRMS (EI) exact mass calcd for ($C_{11}H_{16}O_3$) requires *m/z* 196.1099, found *m/z* 196.1093. $[\alpha]_D$ = +12.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3S, 2'S*) isomer t_r = 12.2 min and (*3R, 2'R*) isomer t_r = 13.8 min.

(*3S,2'R*)-3-(2'-methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-3-phenyl-propionaldehyde (Table 3, entry 4). Prepared according to the general procedure from (*E*)-cinnamaldehyde (378 μL, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2

mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and trichloroethylene (4.0 mL) at −40 °C for 30 h to provide the title compound as a colorless oil (177.1 mg, 77% yield, 6 : 1 dr, 99% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2831, 2722, 1757, 1723, 1602, 1602, 1493, 1454, 1378, 1226, 1106, 953.2, 820.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO), 7.34-7.16 (m, 5H, $C_5\mathbf{H_5}$), 7.31 (d, *J* = 6.0 Hz, 1H, C**H**CHCO$_2$), 5.98 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 3.50 (dd, , *J* = 5.5, 8.2 Hz, 3H, C**H**Ph), 2.84 (ddd, *J* = 1.6, 8.8, 18.1 Hz, 1H, C**H**$_2$CHO), 2.84 (ddd, *J* = 1.1, 5.5, 18.1 Hz, 1H, C**H**$_2$CHO), 1.22 (s, 3H, $OCCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 172.3, 161.0, 138.4, 129.5, 128.8, 127.9, 120.9, 90.2, 46.1, 44.7, 22.4; HRMS (CI) exact mass calcd for ($C_{14}H_{14}O_3$) requires *m/z* 230.0943, found *m/z* 230.0934. $[\alpha]_D$ = +69.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3R, 2'R*) isomer t_r = 61.7 min and (*3S, 2'S*) isomer t_r = 64.0 min.

(*2S,2'R*)-Benzoic acid 2-(2'-methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-4-oxo-butyl ester (Table 3, entry 5). Prepared according to the general procedure from (*E*)-4-benzyloxy-but-2-enal (571 mg, 3.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), (*2S*, *5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (4.0 mL) at −70 °C for 24 h to provide the title compound as a colorless oil (248.8 mg, 86% yield, >20 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3071, 2982, 2939, 2849, 2736, 1758, 1721, 1602, 1452, 1384, 1315, 1273, 1177, 1112, 1071, 1026, 952.4, 822.7, 712.5 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 9.76 (s, 1H, CHO), 7.93 (d, *J* = 7.1 Hz, 2H, Ar), 7.60-7.38 (m, 4H, Ar, C**H**CHCO$_2$), 6.07 (d, *J* = 6.0 Hz, 1H, CHC**H**CO$_2$), 4.41 (dd, *J* = 4.9, 12.1 Hz, 1H, OC**H**$_2$), 4.22 (dd, *J* = 5.5, 12.1 Hz, 1H, OC**H**$_2$), 3.04-2.94 (m, 1H, CH$_2$C**H**CH$_2$), 2.72-2.54 (m, 2H, C**H**$_2$CHO), 1.54 (s, 3H, CC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 171.7, 166.1, 159.0, 133.7, 129.7, 129.4, 128.8, 121.5, 89.1, 63.9, 41.5, 39.4, 23.8; HRMS (CI) exact mass calcd for ($C_{16}H_{16}O_5$) requires *m/z* 288.0998, found *m/z* 288.1003. [α]$_D$ = +45.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (10% ethanol / hexanes, 1 mL/min); (*2S, 2'R*) isomer t$_r$ = 47.9 min and (*2R, 2'S*) isomer t$_r$ = 67.0 min.

(*2S,2'R*)-2-(2'-methyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-4-oxo-butyric acid methyl ester (Table 3, entry 6). Prepared according to the general procedure from (*E*)-methyl-4-oxo-butenoate **9** (228.2 mg, 2.00 mmol), trimethyl-(5-methyl-furan-2-yloxy)-silane (184 μL, 1.00 mmol), *(2S, 5S)*-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and trichloroethylene (2.0 mL) at −60 °C for 22 h to provide the title compound as a colorless oil (178.2 mg, 84% yield, 11 : 1 dr, 99% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3434, 3085, 2954, 2849, 2725, 1760, 1734, 1604, 1437, 1364, 1245, 1172, 1112, 1094, 1045, 956.3, 821.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, CHO), 7.58 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 6.05 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 3.72 (s, 3H, OCH_3), 3.17-2.79 (m, 3H, C**H**C**H**$_2$CHO), 1.42 (s, 3H, $OCCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 171.3, 170.7, 160.0, 120.7, 87.0, 52.9,

46.8, 41.7, 21.0; HRMS (CI) exact mass calcd for ($C_{10}H_{12}O_5$) requires *m/z* 212.0684, found *m/z* 212.0685. $[\alpha]_D$ = +50.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-DM (30 m x 0.25 mm) column (130 °C isotherm, 1 mL/min); (*2R, 2'S*) isomer t_r = 48.6 min and (*2S, 2'R*) isomer t_r = 50.8 min.

(*3S,2'R*)-4-Methyl-3-(5-oxo-2,5-dihydro-furan-2-yl)-pentanal (Table 4, entry 1). Prepared according to the general procedure from (*E*)-4-methyl-2-pentenal (351 μL, 3.00 mmol), 2-(trimethylsilyloxy)furan (168 μL, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), dichloroacetic acid (16.5 μL, 0.20 mmol), H_2O (90.0 μL, 5.00 mmol), and $CHCl_3$ (1.91 mL) at −50 °C for 7 h to provide the title compound as a colorless oil (127.2 mg, 70% yield, 7.3 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2963, 2870, 2821, 2731, 1753, 1721, 1599, 1467, 1391, 1372, 1325, 1265, 1250, 1163, 1103, 1024, 985.4, 905.2, 819.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H, CHO), 7.39 (dd, *J* = 1.4, 5.5 Hz, 1H, C**H**CHCO$_2$), 6.10 (dd, *J* = 1.6, 5.8 Hz, 1H, CHC**H**CO$_2$), 5.22 (m, 1H, OCH), 2.47-2.23 (m, 2H, CH_2), 1.97-1.82 (m, 1H, $CHMe_2$), 1.03 (d, *J* = 6.6 Hz, 3H, CH(C**H$_3$**)$_2$); 0.99 (d, *J* = 6.9 Hz, 3H, CH(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 173.1, 156.8, 122.0, 84.0, 40.7, 40.3, 30.4, 20.7, 20.3; HRMS (CI) exact mass calc'd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0937. $[\alpha]_D$ = −87.4 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-DM (30 m x 0.25 mm) column (170 °C isotherm, 1 mL/min); (*3R, 2'S*) isomer t_r = 6.7 min and (*3S, 2'R*) isomer t_r = 7.0 min.

(*3R,2'R*)-3-(2'-Ethyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-butyraldehyde (Table 4, entry 3). Prepared according to the general procedure from (*E*)-crotonaldehyde (248 μL, 3.00 mmol), trimethyl-(5-ethyl-furan-2-yloxy)-silane (184 mg, 1.00 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (49.2 mg, 0.200 mmol), 2,4-dinitrobenzoic acid (42.4 mg, 0.20 mmol), H_2O (36.0 μL, 2.00 mmol), and CH_2Cl_2 (6.0 mL) at −70 °C for 11 h to provide the title compound as a colorless oil (155.7 mg, 83% yield, 16 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 3093, 2978, 2929, 2874, 2722, 1759, 1724, 1602, 1460, 1384, 1218, 1124, 975.9, 918.7, 822.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (t, *J* = 1.6 Hz, 1H, CHO), 7.26 (d, *J* = 5.5 Hz, 1H, C**H**CHCO$_2$), 6.00 (d, *J* = 5.5 Hz, 1H, CHC**H**CO$_2$), 2.58-2.46 (m, 1H, C**H**CH$_3$), 2.38 (dd, *J* = 3.8, 17.6 Hz, 1H, C**H**$_2$CHO), 2.07 (ddd, *J* = 1.6, 8.8, 17.0 Hz, 1H, C**H**$_2$CHO), 1.90- 1.60 (m, 2H, C**H**$_2$CH$_3$), 0.85 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.68 (t, *J* = 7.1 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 172.4, 157.7, 122.6, 93.4, 45.6, 33.5, 28.2, 16.0, 7.7; HRMS (CI) exact mass calc'd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0942. $[\alpha]_D$ = +25.5 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (150 °C isotherm, 1 mL/min); (*3S, 2'S*) isomer t_r = 27.0 min and (*3R, 2'R*) isomer t_r = 29.8 min.

(*2S,1'R*)-2-(1'-methyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (Table 4, entry 4). Prepared according to the general procedure from (*E*)-crotonaldehyde (81.0 μL, 0.981 mmol), 5-triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (97.5 mg, 0.327 mmol), the trifluoroacetic acid salt of (*2S, 5S*)-5-

benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (23.6 mg, 0.065 mmol), H_2O (12.0 μL, 0.654 mmol), and THF (3.3 mL) at −10 °C for 44 h to provide the title compound as a colorless oil (60.0 mg, 86% yield, 6 : 1 dr, 98% ee) after silica gel. IR (film): 3099, 2960, 2737, 1774, 1738, 1260, 1118, 1040, 908.8, 822.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J* = 0.9 Hz, 1H, CHO), 7.40 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.19 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.77 (s, 1H, CO_2CH_3), 3.05 (ddq, *J* = 6.6, 3.9, 3.9 Hz, 1H, C**H**CH_2), 2.63 (dd, *J* = 18.0, 3.9 Hz, 1H, CHC**H**HCHO),), 2.49 (ddd, *J* = 18.0, 3.9, 1.2 Hz, 1H, CHCH**H**CHO), 0.83 (t, *J* = 6.6 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 171.0, 167.6, 153.6, 122.6, 91.9, 53.4, 45.9, 32.4, 13.9; HRMS (CI) exact mass calc'd for ($C_{10}H_{13}O_5$) requires *m/z* 213.0763, found *m/z* 213.0763. $[\alpha]_D$ = −59.1 (c = 1.4, $CHCl_3$). The diastereomeric ratio was determined by ^1H NMR. The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (165 °C isotherm, 0.8 mL/min); *(2S,1'R)* isomer t_r = 16.8 min, *(2R,1'S)* isomer t_r = 19.2 min.

(*2R,1'R*)-2-(1'-methyl-3'-oxo-propyl)-5-oxo-2,5-dihydrofuran-2-carboxylic acid methyl ester (Table 4, entry 5). Prepared according to the general procedure from (*E*)-crotonaldehyde (81.0 μL, 0.98 mmol), 5-triisopropylsilanyloxy-furan-2-carboxylic acid methyl ester **6** (97.2 mg, 0.33 mmol), the trifluoromethanesulfonic acid salt of *(2S, 5S)*-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (25.8 mg, 0.065 mmol), H_2O (11.7 μL, 0.65 mmol), and $CHCl_3$ (3.3 mL, 0.1 M) at −10 °C for 4 d to provide the title compound as a colorless oil (60.2 mg, 83% yield, 7 : 1 dr, 98% ee) after silica gel. IR (film): 3099, 2960, 2734, 1773, 1738, 1254, 1117, 1038, 908.2, 821.5 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 9.67 (s, 1H, C**H**O), 7.38 (d, *J* = 5.4 Hz, 1H, CH=C**H**), 6.14 (d, *J* = 5.4 Hz, 1H, C**H**=CH), 3.79 (s, 1H, $CO_2C\mathbf{H_3}$), 3.04 (ddq, *J* = 7.2, 6.6, 5.7 Hz, 1H, **CH**CH_2), 2.45 (dd, *J* = 18.6, 5.4 Hz, 1H, C**H**HCHO), 2.32 (ddd, *J* = 18.0, 7.2, 0.9 Hz, 1H, CH**H**CHO), 0.83 (t, *J* = 6.6 Hz, 3H, CHC$\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 170.8, 167.3, 154.2, 122.3, 92.1, 53.4, 44.3, 32.5, 15.9; HRMS (EI) exact mass calc'd for ($C_{10}H_{12}O_5$) requires *m/z* 212.0684, found *m/z* 212.0682. $[\alpha]_D$ = −79.5 (c = 1.4, $CHCl_3$). The diastereomeric ratio was determined by ^{1}H NMR. The enantiomeric ratio was determined by GLC analysis of the aldehyde using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (165 °C isotherm, 0.8 mL/min); *(2R,1'R)* isomer t_r = 17.9 min, *(2S,1'S)* isomer t_r = 19.7 min.

(*3R,2'R*)-3-(2',4'-Dimethyl-5'-oxo-2',5'-dihydro-furan-2'-yl)-butyraldehyde

(Table 4, entry 6). Prepared according to the general procedure from (*E*)-crotonaldehyde (124 μL, 1.50 mmol), trimethyl-(3,5-dimethyl-furan-2-yloxy)-silane (102 mg, 0.500 mmol), (*2S, 5S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol), 2,4-dinitrobenzoic acid (21.2 mg, 0.20 mmol), H_2O (18.0 μL, 1.00 mmol), and CH_2Cl_2 (2.0 mL) at −65 °C for 23 h to provide the title compound as a colorless oil (66.5 mg, 73% yield, 24 : 1 dr, 90% ee) after silica gel chromatography (40% EtOAc/hexanes). IR (film) 2980, 2929, 2885, 2831, 2732, 1754, 1723, 1662, 1449, 1378, 1324, 1258, 1138, 1089, 1069, 1051, 999.8, 941.6, 876.1, 761.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (dd, *J* = 1.1, 2.2 Hz, 1H, CHO), 6.95 (q, *J* = 1.6 Hz, 1H, C**H**CCH_3CO_2), 2.54-2.40 (m, 2H, C**H**C$\mathbf{H_2}$CHO), 2.15 (ddd, *J* = 2.2, 9.3, 17.6 Hz, 4H, C$\mathbf{H_2}$C$\mathbf{H_2}$), 1.86 (d, *J* = 1.6 Hz, 3H, C$\mathbf{H_3}CCO_2$), 1.39 (s, 3H, $OCCH_3$), 0.94 (d, *J* = 7.1 Hz,

3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 200.8, 173.3, 151.2, 130.3, 88.2, 46.0, 35.3, 23.2, 16.2, 11.0; HRMS (CI) exact mass calcd for ($C_{10}H_{14}O_3$) requires *m/z* 182.0943, found *m/z* 182.0933. $[]_D$ = +22.3 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex -TA (30 m x 0.25 mm) column (130 °C isotherm, 1 mL/min); (*3R, 2'R*) isomer t_r = 48.9 min and (*3S, 2'S*) isomer t_r = 61.9 min.

(2*S*,3*R*)-5-(*N*-Methyl-*N*-((*S*)-1-phenylethyl)amino)-2-(benzamido)-2,3-dimethylpentanoic Acid•Hydrochloride (26). To a 2-dram vial equipped with a magnetic stir bar and charged with **23** (0.36 mmol, 87.9 mg) was added THF (1.4 mL) and (*S*)-*N*-dimethylbenzylamine (0.54 mmol, 78.3 L). To this solution was added $Na(AcO)_3BH$ (0.54 mmol, 113.9 mg) in one portion. The resulting heterogeneous solution was stirred for 5 min, at which time it was determined to be complete by TLC. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ and stirred for 12 h. The solution was then extracted with CH_2Cl_2 (3 x 4 mL); the organics were dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (1/1 EtOAc/hexanes) to provide (*S*)-4-((*R*)-4-(*N*-methyl-*N*-((*S*)-1-phenylethyl)amino)butan-2-yl)-4-methyl-2-phenyloxazol-5(4H)-one (117.5 mg). ^{1}H NMR (300 MHz, $CDCl_3$) 8.04-7.97 (m, 2H, ArH), 7.57 (tt, *J* = 2.6, 10.0 Hz, 1H, ArH), 7.48 (tt, *J* = 2.6, 7.0 Hz, 2H, ArH), 7.32-7.18 (m, 5H, ArH), 3.51 (q, *J* = 6.7 Hz, 1H, CHPh), 2.46 (ddd, *J* = 8.2, 8.2, 12.3 Hz, 1H, C**H**$_2$N), 2.46 (ddd, *J* = 4.1, 8.5, 12.3 Hz, 1H, C**H**$_2$N), 2.17 (s, 3H, NCH_3), 2.09-1.96 (m, 1H, C**H**$_2$$CH_2$N), 1.94-1.80 (m, 1H, C**H**$_2$$CH_2$N), 1.35 (d, *J* = 6.7 Hz, 3H, C**H**$_3$CHN), 1.32-1.19 (m, 1H, C**H**CH_2CH_2N), 0.84 (d, *J* = 6.7 Hz, 3H, CH_3CCO_2); ^{13}C NMR (75 MHz, $CDCl_3$) 181.1, 160.0, 144.2, 132.8,

129.0, 128.3, 128.1, 127.9, 127.0, 126.3, 72.8, 64.0, 52.3, 38.3, 38.2, 28.1, 22.0, 19.2, 14.0. To a 2-dram vial equipped with a magnetic stir bar and charged with (*S*)-4-((*R*)-4-(*N*-methyl-*N*-((*S*)-1-phenylethyl)amino)butan-2-yl)-4-methyl-2-phenyloxazol-5(4H)-one (0.32 mmol, 115.3 mg) was added ether (0.5 mL). To this solution was added 2M hydrochloric acid in ether (173 □L), at which time a white precipitate formed and was filtered to produce the title compound (111.6 mg, 87% yield). HRMS (CI) exact mass calcd for ($C_{10}H_{14}O_3$) requires *m/z* 308.1808, found *m/z* 308.1819. Recrystallization from tetrahydrofuran/ether afforded crystals suitable for single X-ray diffraction.

V. References

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Chapter 4

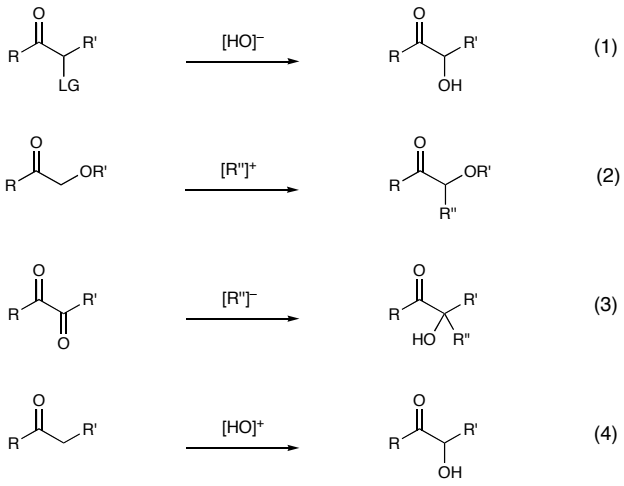
Enantioselective Organocatalytic α-Oxidation of Aldehydes

I. Introduction

α-Oxidation of Carbonyls

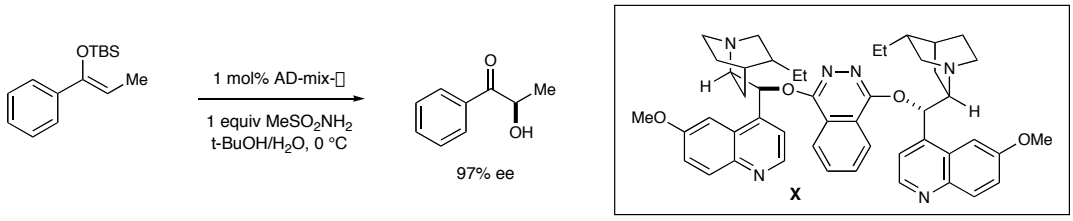
The α-Oxy carbonyl synthon is an important structural motif present in a range of natural isolates of diverse structure and function, including carbohydrates, antibiotics, alkaloids, and terpenes.[1] This asymmetric architecture is also useful for directing further stereoselective elaboration. There are several naturally occurring α-hydroxy acids, but their structural diversity is limited. Four possible strategies for preparation of enantioenriched α-oxy carbonyls have been developed (Scheme 1).[1] The classical method involves displacement of a leaving group, usually derived from α-amino or α-halocarbonyls, with a nucleophilic oxygen source (eq 1). α-Alkylation is an approach in which asymmetric induction from chiral auxiliaries can be utilized (eq 2). Asymmetric hydride reduction of dicarbonyl compounds has also been used to furnish chiral α-oxy carbonyls (eq 3). The most common method is oxidative introduction of the oxygen functionality, in which an enolate reacts with an electophilc oxygen source (eq 4).

Scheme 1. Strategies for the preparation of α-oxy carbonyl compounds

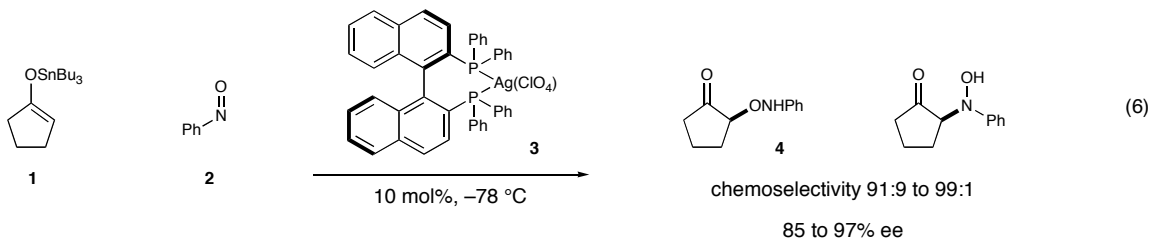


Enantioselective Catalytic Approaches to the α-Oxidation of Carbonyls

Oxidative approaches have proved the most fruitful route to accessing α-oxy carbonyls in an enantioselective catalytic fashion. One of the most widely used approaches is the Rubottom oxidation,[2,3] which generally involves the epoxidation or dihydroxylation of silyl enol ethers. Sharpless's dihydroxylation technology has been readily utilized for these transformations (eq 5).[4] Yamamoto's group has made a recent advance in this area of research, in which they have utilized a tin enolate **1** and the oxidant nitrosobenzene (**2)** in the presence of a BINAP $AgClO_4$ catalyst **3** to generate the α-oxy carbonyl **4** chemo- and enantioselectively (eq 6).[5,6] Both of these methods are limited by the need to use preformed enolates and toxic metals (eq 5, 6; Os, Sn).

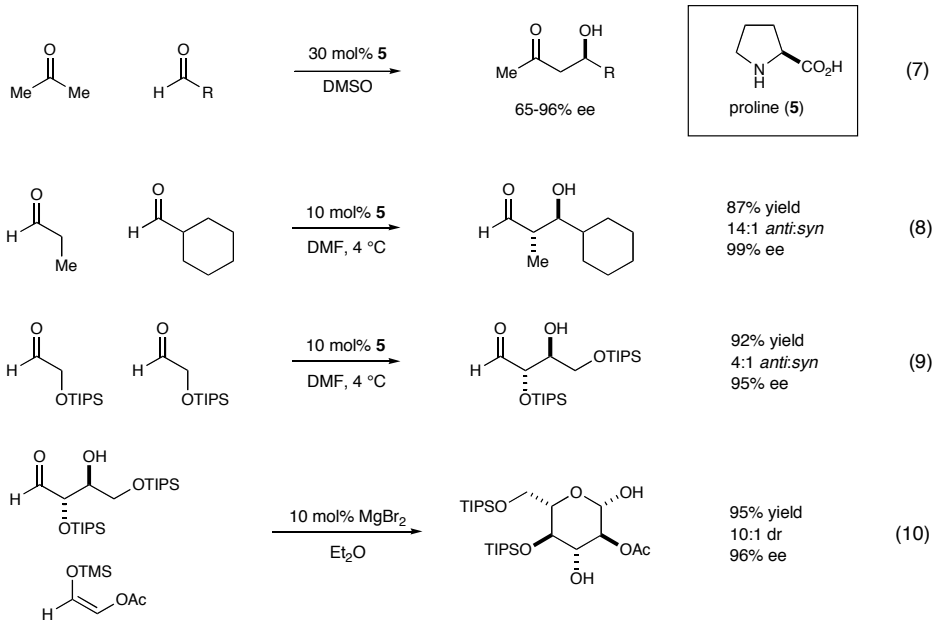


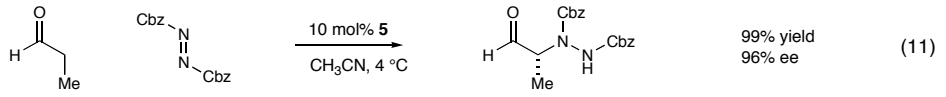
(5)



Proline Catalyzed Reactions

Asymmetric catalysis utilizing the bifunctional catalyst proline (**5**) has entered a second renaissance since its rediscovery by Lerner, Barbas, and List for the enantioselective intermolecular aldol reaction (eg 7).[7-9] The MacMillan group utilized this highly flexible catalytic platform to perform the first enantioselective aldehyde–aldehyde aldol reaction (eq 8).[10] This chemistry was further expanded to access protected erythoses by aldol dimerization of protected α-oxyaldehydes (eq 9),[11] which through a subsequent metal mediated aldol reaction provided protected hexoses (eq 10).[12] Recently, the List[13] and Jørgensen[14] groups have developed highly efficient and enantioselecetive α-amination procedures that utilize azodicarboxylates as an electrophilic source of nitrogen (eq 11).

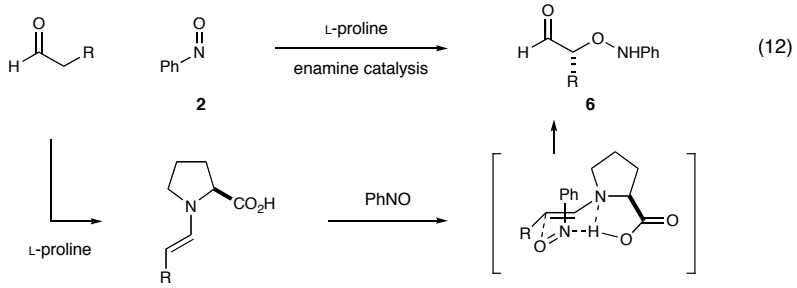




II. Results and Discussion

Organocatalyzed α-Oxidation of Carbonyls

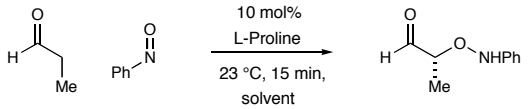
The α-oxy carbonyl synthon has proven its utility as a synthetic intermediate and is ubiquitous in natural isolates. However, asymmetric catalytic α-oxidations of carbonyls have previously relied exclusively upon the use of pre-formed enolates or enolate equivalents. Yamamoto and coworkers recently disclosed a conceptually novel approach to the enantioselective oxidation of tin enolates using nitrosobenzene (**2**) as an electrophilic source of oxygen (eq 6).[5,6] Accordingly, we hypothesized that L-proline (**5**) could participate in a HOMO-raising enamine activation of an aldehyde while simultaneously partaking in LUMO-lowering protonation of the Brønsted basic nitrogen of nitrosobenzene (**2**), furnishing α-oxidized aldehydes with high enantiocontrol (eq 12).



Our initial studies revealed that the proposed organocatalytic α-oxyamination is indeed facile at room temperature, and can be accomplished using a variety of reaction conditions (Table 1). While variation of solvent had a pronounced effect on reaction rate (*cf.* entries 1 and 2 vs. entries 8 and 9), excellent levels of enantioselection were observed for a diverse range of dielectric media. Notably, suppression of the homodimerization

aldol[10] and the α-amination pathway was accomplished using $CHCl_3$ to provide the desired α-oxy aldehyde in 78% yield and 96% ee (entry 9). As might be expected, improved selectivities were observed at lower temperature (4 °C), thus defining the optimal conditions to investigate the scope of this new transformation.

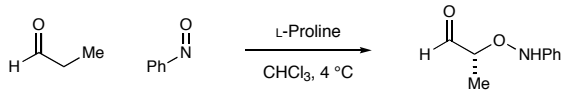
Table 1. Effect of solvent on the asymmetric α-oxyamination



entry	solvent	% yield	% ee
1	dioxane	8	97
2	EtOAc	18	95
3	THF	24	97
4	DMSO	35	94
5	DMF	46	97
6	NMP	50	98
7	CH_3CN	67	96
8	PhH	67	97
9	$CHCl_3$	78	96

The effect of catalyst loading on reaction efficiency was next evaluated (Table 2). Remarkably, catalyst loadings as low as 0.5 mol% can be utilized without significant loss in enantiocontrol (entry 5, 94% ee). In terms of operational convenience, the use of 2 mol% L-proline ensures high levels of reaction efficiency and enantioselectivity while maintaining expedient reaction times (entry 2, 5 mol% L-proline, 86% yield, 97% ee, <1 h).

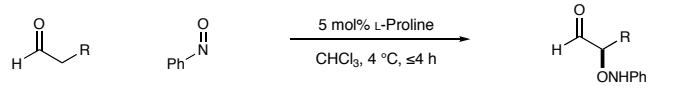
Table 2. Effect of catalyst loading on organocatalyzed α-oxidation

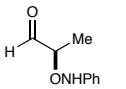
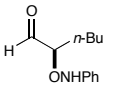
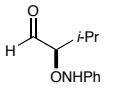
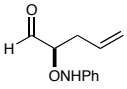
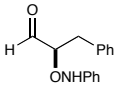
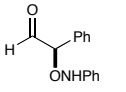
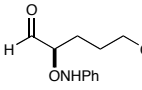
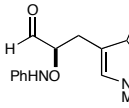


entry	mol% L-Proline	time	% yield	% ee
1	10	20 min	88	97
2	5	45 min	86	97
3	2	2 h	88	97
4	1	8 h	83	97
5	0.5	18 h	68	94

Experiments that probe the scope of the aldehyde substrate are summarized in Table 3. Considerable variation in the steric demand of the aldehyde component (R = Me, Bu, *i*-Pr, and Ph, entries 1–3 and 6) is possible without loss in efficiency or enantiocontrol (70–88% yield, 97 to 99% ee). Notably, these mild reaction conditions allow the use of electron rich π-systems that are typically prone to oxidative degradation. For example, enamine oxidation to access enantioenriched α-oxy aldehydes can be selectively accomplished with substrates that incorporate olefinic or indolic functionality (entry 4 and 8; ≥80% yield, ≥98% ee).

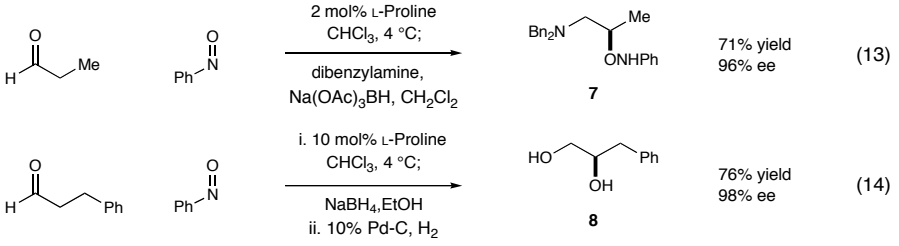
Table 3. Enantioselective α-oxyamination: substrate scope



entry	R	product	% yield	% ee
1	Me		88	97
2	*n*-Pr		79	98
3	*i*-Pr		85	99
4	CH_2CHCH_2		80	99
5	CH_2Ph		95	97
6	Ph		60	98
7	$(CH_2)_3OTIPS$		76	98
8	CH_2(3'-indolyl)		83	98

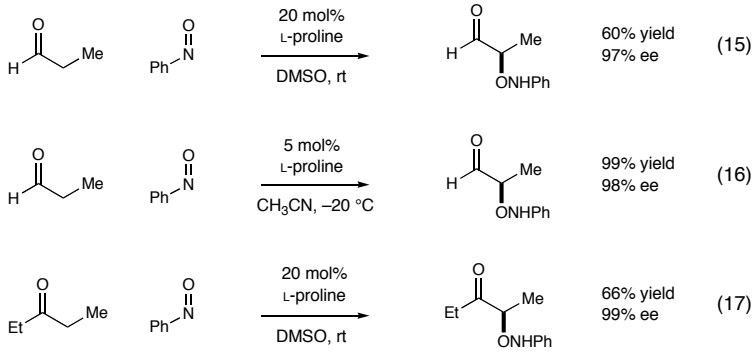
The α-oxy aldehyde products are oligomeric in solution and were most conveniently isolated as the corresponding primary alcohols. Nonetheless, these oligomeric aldehydes smoothly undergo reactions typical of aldehydes. For example, treatment of the unpurified oxyamination product of propanal with dibenzylamine and sodium triacetoxyborohydride provides the 1,2-amino alcohol **7** in high yield and with excellent enantioselectivity (eq 13). Furthermore, a convenient one-pot procedure highlights the utility of this organocatalytic protocol as a dihydroxylation surrogate. Specifically, reduction of the oxyamination product with $NaBH_4$, followed by N–O bond hydrogenolysis provides the corresponding terminal diol **8** in 74% yield and 98% ee (eq 14). With respect to operational convenience, it should be noted that all reactions

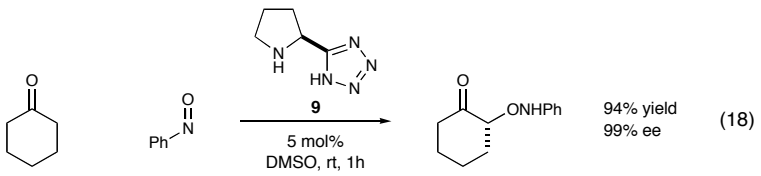
performed in this study were conducted in an aerobic atmosphere with unpurified solvents.



Other Approaches to Organocatalyzed α-Oxidation of Carbonyls[15]

After our report of the first direct α-oxidation of aldehydes, several other groups reported similar methodologies. The Zhong[16-18] and Hayashi[19] groups published virtually the same methodology, differing only by the conditions under which the proline-catalyzed α-oxidation were run (eq 15, 16). Several other groups have demonstrated the proline catalyzed nitrosobenzene oxidation of ketones, in which slow addition of nitrosobenzene (**2**) was necessary to achieve good levels of reaction efficiency (eg 17).[20-22] Yamamoto has described a tetrazole proline derivative **9** that provides excellent levels of reaction efficiency and enantioselectivity for the nitrosobenzene oxidation of aldehydes and ketones (eq 18).[23]





Blackmond's α-Oxidation Mechanism

In addition to the synthetic interest, the Blackmond group focused their attention on the mechanism of the α-oxidation reaction (eq 12) and studied the proline-catalyzed process by reaction calorimetry.[24-26] It was observed that the rate of the reaction increased as the reaction progressed (Figure 1). Along with this unusual kinetic profile, it was also found that when non-enantiopure proline was used as a catalyst, the enantiomeric excess of the product was greater than expected for a linear relationship (Figure 2). With these results, the Blackmond group stated that this was the first fully organic reaction possessing rate acceleration and a non-linear effect, both of which are important to the chemical rational for the evolution of biological homochirality.

Figure 1. Blackmond's reaction calorimetry data[26]

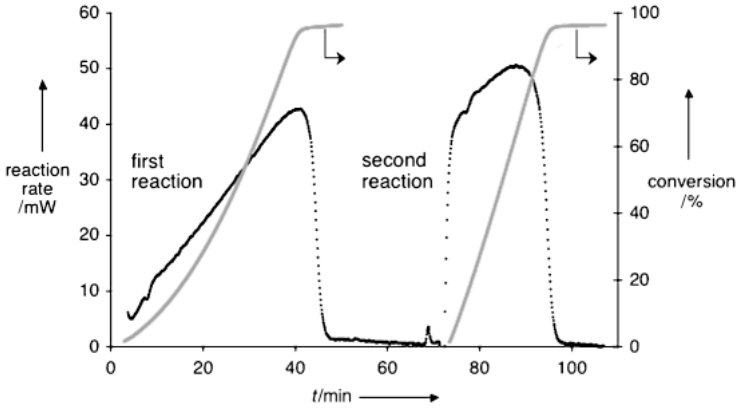
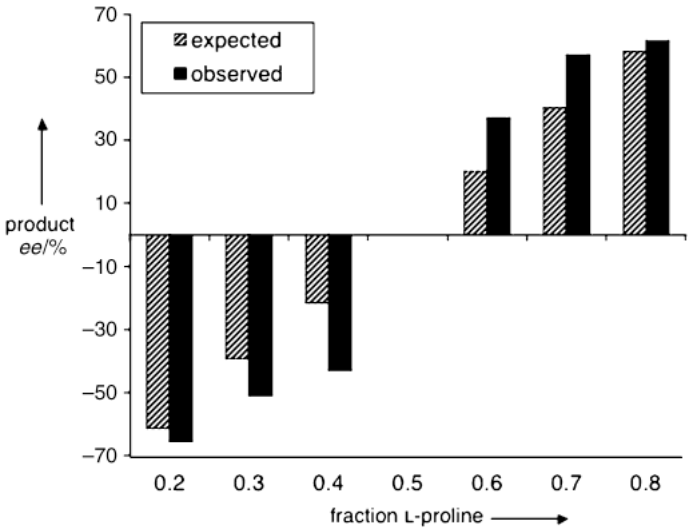
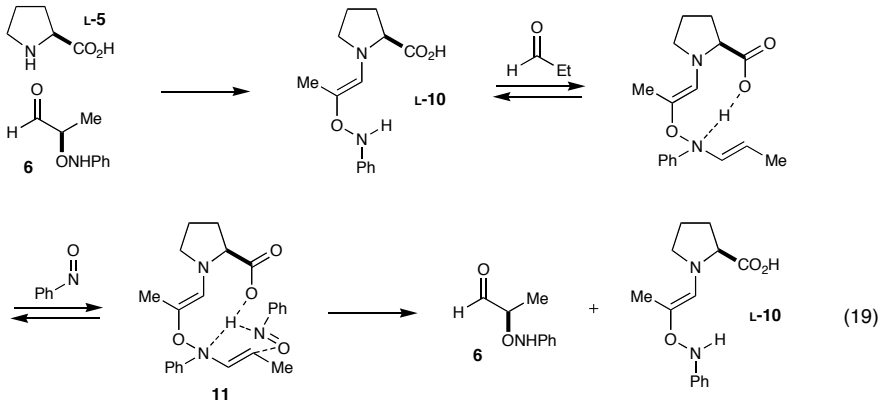


Figure 2. Blackmond's non-linear relationship data[26]



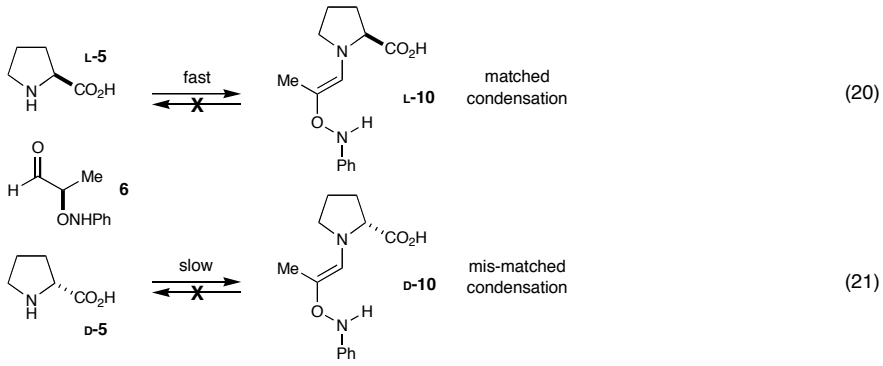
The rate acceleration and the non-linear effect were thus rationalized by proposing an autoinductive mechanism in which the product **6** condenses with proline (**L-5**) to from an improved catalyst **L-10** (eq 19).[26] It is key to the Blackmond group's proposed mechanism that the new catalytic species **L-10** is a more active catalyst than proline (**L-5**). The □-oxygen increases the nucleophilicity of the nitrogen due to the "alpha effect"[27] providing a more reactive catalyst toward condensation to propionaldehyde generating dienamine **11** (eq 19). Nitrosobenzene then undergoes reaction with dienamine **11** to generate the product **6** and reconstitute the proposed catalyst **L-10**.

Blackmond's proposed autoinductive mechanism



(19)

Blackmond's proposed mechanism for asymmetric amplification



(20)

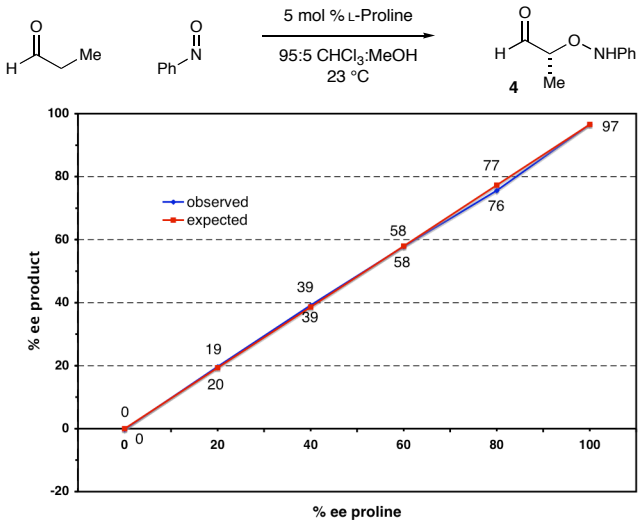
(21)

The Blackmond group also proposed that the asymmetric amplification could be explained by a mechanism of product mediated kinetic resolution of proline. If the condensation of L-proline (**L-5**) with the product **6** (eq 19) is much faster than the condensation of D-proline (**D-5**) with **6** (eq 20), then a greater concentration of the improved catalyst **L-10** will be generated leading to a non-linear relationship between the enantiomeric excesses of **6** and proline (**5**). Due to the fact that the reverse of the equilibriums in equation 20 and 21 would lead to racemic product **6**, the Blackmond group stated that the formation of the improved catalyst **10** must be "virtually irreversible on the reaction timescale, since product racemization was not observed."[26]

The Role of Proline Solubility

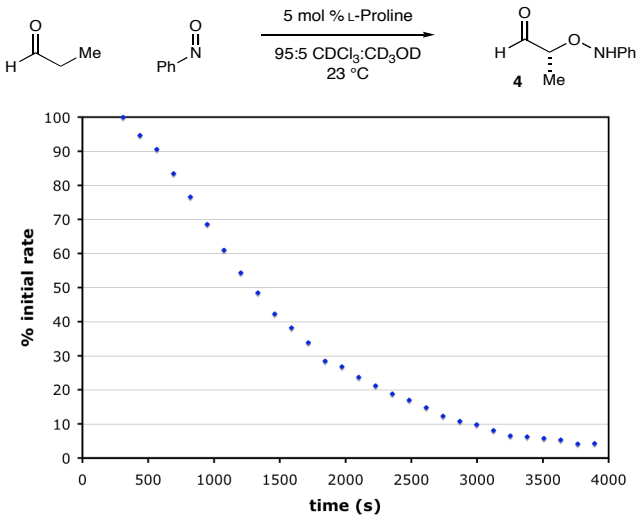
The mechanistic requirement that the condensation that generates the proposed catalyst **10** must be virtually irreversible, as well as the Blackmond group providing no structural data for the existence of the proposed catalyst **10**, lead us to evaluate in detail the rate acceleration and non-linear effect observed for the proline-catalyzed □-oxidation reaction (eq 12). Upon attempting to reproduce the non-linear effect, we found that indeed, there was a non-linear relationship, but it was very irreproducible. In fact, both positive and negative non-linear effects were observed. We hypothesized that the heterogeneous nature of the reaction was leading to the irreproducibility. Since proline is barely soluble in many organic solvents, but possesses much higher solubility in methanol, addition of 5% by volume methanol to the reaction solvent ($CHCl_3$) completely solubilized the proline, generating a homogeneous solution. Under these reaction conditions, both the enantiomeric excesses of the product **6** and proline (**5**) followed a linear relationship (Figure 3).

Figure 3. Enantiomeric excess of the product **6** vs. the enantiomeric excess of proline (**5**)



Since the homogeneous reaction conditions produced linear behavior, we became interested in evaluating the kinetics of the nitroso aldol reaction under the homogeneous reaction conditions. ^{1}H NMR was utilized to study the rate of propionaldehyde consumption as the nitroso aldol reaction progressed. Intriguingly, the first rate measured was the greatest and every subsequent rate decreased (Figure 4). The observed decrease in rate as the reaction progressed is in complete contrast to that observed under the heterogeneous conditions, but consistent with normal kinetic models that do not involve an autoinductive mechanism

Figure 4. The percent intial rate of homogeneous reaction as a function of time

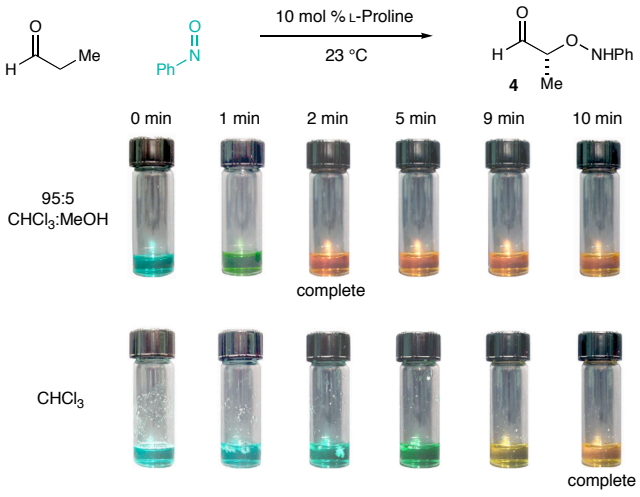


Due to the homogeneous and heterogeneous conditions of the proline-catalyzed α-oxidation reactions having displayed two very different reaction profiles, we became interested in comparing both reaction conditions directly. The highly colored nature of nitrosobenzene in solution allows qualitative visual comparison (Figure 5). The vials at time 0 contain proline, nitrosobenzene, and solvent. Addition of propionaldehyde under homogeneous reactions conditions (upper vials, 95:5 $CHCl_3$:MeOH) produced a rapid

reaction, in which the color of the solution changed from blue to the orange endpoint in 2 minutes. In contrast, the heterogeneous reaction was 5 fold slower and the oxyamination proceeded to completion within 10 minutes.

More interestingly, proline was observed to dissolve as the reaction progressed (Figure 5, lower vials, $CHCl_3$). At time 0, proline can be seen as an insoluble white particulate, but as the reaction proceeded, the proline was solubilized, increasing its concentration in solution. Assuming rate is directly related to the concentration of proline, the observed rate acceleration under the heterogeneous reaction conditions is due to the concentration of proline in solution continually being increased as the reaction progressed. The increased solubility was attributed to the polarity of the reaction solution increasing with product formation.

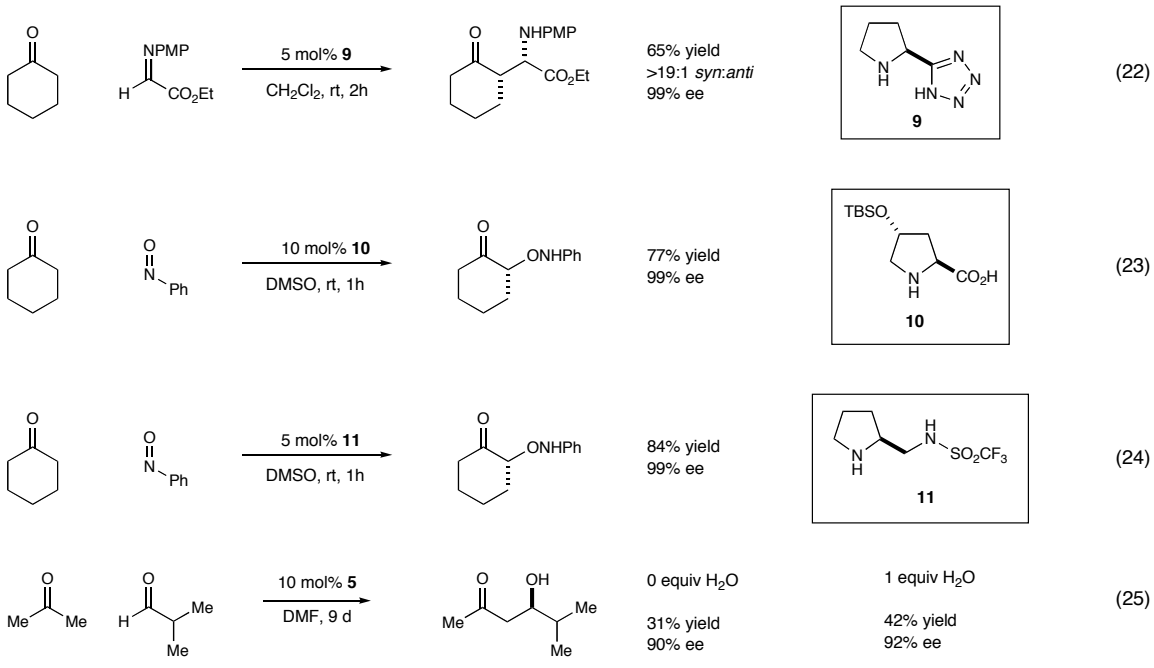
Figure 5. Visual comparison of the homogeneous and heterogeneous reactions



Soluble Proline Mimics

Other groups have noticed that the low solubility of proline has a detrimental effect on the rate of the proline-catalyzed reactions. The Yamamoto[23,28,29] and Ley[30-32]

groups have simultaneously developed tetrazole proline derivative **9** designed to increase the solubility of the catalyst in organic solvents (eq 17, 22). The TBS derivative of *trans*-4-hydroxy-L-proline **10** (eq 23)[33] and the pyrrolidine sulfonamide **11** (eq 24)[34] also afford catalyst systems with increased solubility providing increased rate of oxidation. The addition of water to the reaction media has provided increased rate in the proline-catalyzed aldol reaction, most likely due to increased solubility of proline in the DMSO solution (eq 25).[35]



III. Conclusion

In summary, we have described the first direct, enantioselective α-oxidation of aldehydes.[36] This technology has provided rapid access to terminal diols and 1,2-amino alcohols. Furthermore, experiments have described how both the rate acceleration and the non-linear relationship observed by Blackmond under heterogeneous conditions of

the proline-catalyzed □-oxidation reaction are due to the low solubility of proline in $CHCl_3$.

IV. Experimental Section

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[37] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[38] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralcel AD column (1.6 x 25 cm) and AD guard (1.6 x 5 cm), Chiralcel OD H (1.6 x 25 cm) and OD guard (1.6 x 5 cm), or Chiralcel AS (1.6 x 25 cm) and AS guard (1.6 x 5 cm), as noted.

Procedures

General Procedure: To a 2-dram vial equipped with a magnetic stir bar and charged with L-proline was added chloroform (500 μL) and the suspension cooled to 4 °C. The suspension was cooled for 10 minutes before nitrosobenzene (107.1 mg, 1 mmol) was added in one portion, at which time the solution became green. To this green heterogeneous solution was then added the appropriate aldehyde (3 mmol) in one portion. The resulting solution was then stirred at 4 °C until the reaction was determined to be complete by TLC and the disappearance of green color in solution, resulting in a final yellow homogeneous solution. The reaction mixture was then transferred to an ethanol suspension of $NaBH_4$ at 0 °C. After 20 minutes, the reaction was treated with saturated aqueous $NaHCO_3$, extracted with dichloromethane (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was then purified by silica gel chromatography (solvents noted) and fractions concentrated *in vacuo* to provide the title compounds. The enantioselectivity was determined by chiral HPLC analysis.

5-(Triisopropyl-silanyloxy)-pentanal. To a round bottom flask equipped with a magnetic stirring bar was added 5-hydroxypentanal (4.76 mL, 49 mmol), triisopropylsilylchloride (12.6, 58.7 mmol), imidazole (6.67 g, 98 mmol) and CH_2Cl_2. After 4 h, the reaction was treated with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (100 mL, 3x), and dried over sodium sulfate to provide the title compound as a clear oil (1.56 g, 12% yield) after silica gel chromatography (3% EtOAc/ hexanes). IR (film) 2943, 2892, 2867, 2716, 1728, 1463, 1389, 1389, 1248, 1106, 1071, 1014, 995.9, 919.3, 882.5, 792.6, 724.7, 680.1, 658.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.76 (t, J = 1.9 Hz,

1H, CHO), 3.70 (t, *J* = 6.1 Hz, 2H, C**H**$_2$O), 2.46 (dt, *J* = 1.9, 7.2 Hz, 2H, C**H**$_2$CHO), 1.80-1.50 (m, 4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$), 1.04 (d, *J* = 3.5 Hz, 18H, 6(CH_3)), 1.12- 0.98 (m, 3H, 3(C**H**CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) 202.4, 62.7, 43.5, 32.2, 18.6, 17.9, 11.9; HRMS (CI) exact mass calcd for ($C_{14}H_{30}O_2Si$) requires *m*/*z* 258.2015, found *m*/*z* 258.2023.

3-(1-Methyl-1*H*-indol-3-yl)-propionaldehyde. An amber 2-dram vial equipped with a magnetic stir bar and containing (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one•trifluoroacetic acid (1 g, 2.8 mmol) was charged with CH_2Cl_2 (100 mL), then cooled to –50 °C. The solution is stirred for 5 min before acrolein (12.4 mL, 188 mmol) was added. After stirring for an additional 10 minutes, *N*-methylindole (8 mL, 62 mmol) was added in one portion. The resulting suspension was stirred at constant temperature until complete consumption of the *N*-methylindole as determined by TLC analysis (8 hours). The reaction mixture was then transferred cold through a silica gel plug and the filtrates were concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10% EtOAc/ hexanes) to afford the title compound as a yellow oil (3.5 g, 30% yield). IR (film) 3041, 2915, 2836, 2713, 1716, 1558, 1540, 1472, 1458, 1370, 1319, 1242, 1150, 1124, 1062, 1006 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 9.76 (t, *J* = 1.6 Hz, 1H, CHO), 7.70-7.62 (m, 1H, Ar), 7.40-7.18 (m, 3H, Ar), 6.91 (s, 1H, CHN), 3.79 (s, 3H, CH_3), 3.18 (t, *J* = 7.2 Hz, 2H, CH_2Ar), 2.89 (dt, *J* = 1.0, 7.2 Hz, 2H, C**H**$_2$CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 202.1, 136.7, 127.1, 126.0, 121.3, 118.4, 112.6, 109.0, 43.7, 32.0, 17.3; HRMS (CI) exact mass calcd for ($C_{12}H_{13}NO$) requires *m*/*z* 187.0997, found *m*/*z* 187.0991.

(*R*)-2-(*N*-Phenyl-aminooxy)-propan-1-ol (Table 3, entry 1). Prepared according to the general procedure from propionaldehyde (216 μL, 3.00 mmol) for 2 h to provide the title compound as a yellow oil (147.2 mg, 88% yield, 97% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3380, 3275, 2933, 1601, 1493, 1240, 1153, 1045, 898.5, 766.5, 692.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30- 7.22 (m, 2H, ArH), 7.00- 6.92 (m, 3H, ArH), 4.13- 4.20 (m, 1H, CH), 3.76 (dd, 1H, *J* = 3.3, 12.1 Hz, C**H**$_2$), 3.68 (dd, 1H, *J* = 6.6, 12.1 Hz, C**H**$_2$), 1.23 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 128.7, 121.8, 114.3, 79.9, 65.8, 15.4; HRMS (CI) exact mass calcd for ($C_9H_{13}NO_2$) requires *m/z* 167.0946, found *m/z* 167.0952. $[\alpha]_D$ = +1.13 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (10% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 34.4 min and (*R*) isomer t_r = 40.0 min.

(*R*)-2-(*N*-Phenyl-aminooxy)-hexan-1-ol (Table 3, entry 2). Prepared according to the general procedure from hexanal (240 μL, 2.00 mmol) for 2 h to provide the title compound as a yellow oil (165.2 mg, 79% yield, 98% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3388, 3274, 3052, 1602, 1494, 1467, 1379, 1345, 1305, 1242, 1057, 1027, 898.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.7 Hz, 2H, ArH), 7.10- 6.93 (m, 3H, ArH), 3.96- 3.68 (m, 1H, HOC**H**$_2$C**H**), 3.05 (s, 1H, OH), 1.76- 1.22 (m, 6H, $CH_2CH_2CH_2$), 0.92 (t, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 129.2, 122.5, 115.0, 84.3, 65.4, 30.0, 28.3, 23.2, 14.4; HRMS (CI) exact mass calcd for ($C_{12}H_{19}NO_2$) requires *m/z* 210.1494, found *m/z* 210.1501. $[\alpha]_D$ = +19.9 (c = 1.0, $CHCl_3$).

The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (5% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 25.6 min and (*R*) isomer t_r = 28.7 min.

(*R*)-3-Methyl-2-(*N*-phenyl-aminooxy)-butan-1-ol (Table 3, entry 3). Prepared according to the general procedure from isovaleraldehyde (322 μL, 3.00 mmol) for 2 h to provide the title compound as a yellow oil (166.0 mg, 85% yield, 99% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3380, 3260, 3046, 2961, 2873, 1602, 1494, 1469, 1390, 1363, 1234, 1051, 1026, 975.0, 898.7, 764.3, 737.7, 692.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34- 7.20 (m, 3H, ArH, NH), 7.03- 6.94 (m, 3H, ArH), 3.92- 3.76 (m, 2H, CH_2), 3.71 (ddd, J = 2.8, 6.0, 6.0 Hz, 1H, C**H**O), 3.39 (s, 1H, OH), 2.03 (m, 1H, $CHMe_2$), 1.06 (d, J = 6.6 Hz, 3H, CHC**H$_3$**), 1.00 (d, J = 7.1 Hz, 3H, CHC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 128.7, 122.1, 114.7, 88.4, 63.1, 28.6, 18.8, 18.6; HRMS (CI) exact mass calcd for ($C_{11}H_{17}NO_2$) requires m/z 195.1259, found m/z 195.1261. $[\alpha]_D$ = +39.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (5% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 19.5 min and (*R*) isomer t_r = 22.1 min.

(*R*)-2-(*N*-Phenyl-aminooxy)-pent-4-en-1-ol (Table 3, entry 4). Prepared according to the general procedure from pent-4-enal (296 μL, 3.00 mmol) for 2 h to provide the title compound as a yellow oil (155.3 mg, 80% yield, 99% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3383, 3279, 3072, 2916, 1643, 1602, 1493, 1426, 1415, 1348, 1244, 1026, 994.8, 917.0, 740.6, 693.9 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.30- 7.15 (m, 2H, ArH), 7.05 (s, 1H, NH), 7.00- 6.96 (m, 3H, ArH), 5.95- 5.81 (m, 1H, C**H**=CH_2), 5.19- 5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.03 (dddd, *J* = 2.7, 6.6, 6.6, 6.6 Hz, 1H, CH–ON), 3.89- 3.84 (m, 1H, C$\mathbf{H}_2$OH), 3.77 (dd, *J* = 6.0, 12.0 Hz, 1H, C$\mathbf{H}_2$OH), 2.56- 2.31 (m, 2H, C$\mathbf{H_2}$CH=CH_2), 1.80 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 133.9, 128.9, 122.3, 117.6, 114.7, 83.3, 64.5, 34.7; HRMS (CI) exact mass calcd for ($C_{11}H_{15}NO_2$) requires *m/z* 194.1181, found *m/z* 194.1173. $[\alpha]_D$ = +8.0 (c = 0.83, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (5% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 30.6 min and (*R*) isomer t_r = 36.4 min.

(*R*)-3-Phenyl-2-(*N*-phenyl-aminooxy)-propan-1-ol (Table 3, entry 5). Prepared according to the general procedure from hydrocinnamaldehyde (260 μL, 2.00 mmol) for 4 h to provide the title compound as a yellow oil (231.0 mg, 95% yield, 97% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3385, 3278, 3055, 3028, 2937, 2880, 1601, 1494, 1455, 1346, 1307, 1239, 1082, 1069, 1030, 898.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44- 7.20 (m, 7H, ArH), 7.01 (t, *J* = 7.7 Hz, 1H, ArH), 6.86 (d, *J* = 7.7 Hz, 1H, ArH), 4.16 (dddd, *J* = 2.2, 6.6, 6.6, 6.6 Hz, 1H, CH), 3.87 (ddd, *J* = 2.7, 6.6, 12.1 Hz, 1H, C$\mathbf{H}_2$OH), 3.79- 3.70 (m, 1H, C$\mathbf{H}_2$OH), 3.06 (dd, *J* = 6.6, 13.7 Hz, 1H, C$\mathbf{H}_2$Ph), 3.06 (dd, *J* = 7.1, 13.7 Hz, 1H, C$\mathbf{H}_2$Ph), 2.33 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 138.3, 129.8, 129.2, 128.7, 126.7, 122.4, 114.8, 85.4, 64.1, 36.9; HRMS (CI) exact mass calcd for ($C_{15}H_{17}NO_2$) requires *m/z* 244.1338, found *m/z* 244.1344. $[\alpha]_D$ = +43.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a

Chiracel AD and AD guard column (5% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 26.8 min and (*R*) isomer t_r = 28.5 min.

(*R*)-2-Phenyl-2-(*N*-phenyl-aminooxy)-ethanol (Table 3, entry 6). Prepared according to the general procedure from phenylacetaldehyde (351 μL, 3.00 mmol) for 2 h to provide the title compound as a yellow oil (137.4 mg, 60% yield, 99% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3389, 3277, 3032, 2918 1601, 1494, 1453, 1414, 1350, 1309, 1232, 1027, 896.7, 759.0, 696.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.43- 7.24 (m, 7H, ArH), 7.03- 6.95 (m, 4H, NH, ArH), 5.02 (dd, *J* = 3.3, 8.2 Hz, 1H, CH), 4.04- 3.92 (m, 1H, C**H**$_2$), 3.88- 3.77 (m, 1H, C**H**$_2$), 2.66 (dd, *J* = 4.4, 7.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) □ 148.2, 138.0, 129.3, 128.9, 128.7, 127.3, 122.8, 115.3, 86.8, 66.7; HRMS (CI) exact mass calcd for ($C_{14}H_{15}NO_2$) requires *m/z* 229.1103, found *m/z* 229.1110. [□]$_D$ = –140.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (10% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 26.5 min and (*R*) isomer t_r = 35.0 min.

(*R*)- 2-(*N*-Phenyl-aminooxy)-5-(triisopropyl-silanyloxy)-pentan-1-ol (Table 3, entry 7). Prepared according to the general procedure from 5-(triisopropyl-silanyloxy)-pentanal (776 mg, 3.00 mmol) for 2 h to provide the title compound as a yellow oil (267.2 mg, 76% yield, 98% ee) after silica gel chromatography (20% EtOAc/ hexanes). IR (film) 3367, 3261, 2942, 2966 1602, 1494, 1463, 1376, 1243, 1103, 1061, 882.3, 725.2, 689.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.34- 7.23 (m, 2H, ArH), 7.08 (s, 1H, NH), 7.03- 6.95 (m, 1H, ArH), 4.00 (dddd, *J* = 2.6, 6.2, 6.2, 6.2 Hz, 1H, CH), 3.91- 3.66

(m, 4H, C**H**$_2$OH, C**H**$_2$OSi), 2.68 (s, 1H, OH); 1.85- 1.58 (m, 4H, CH_2CH_2), 1.14- 1.02 (m, 21H, $(CH(CH_3)_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 148.6, 129.3, 122.7, 115.1, 84.1, 65.6, 63.4, 29.3, 26.5, 18.3, 12.2; HRMS (CI) exact mass calcd for ($C_{20}H_{37}NO_3Si$) requires *m/z* 367.2543, found *m/z* 367.2549. [□]$_D$ = + 17.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AS and AS guard column (0.2% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 74.0 min and (*R*) isomer t_r = 88.6 min.

(*R*)-3-(1-Methyl-1*H*-indol-3-yl)-2-(*N*-phenyl-aminooxy)-propan-1-ol (Table 3, entry 8). Prepared according to the general procedure from 3-(1-methyl-1*H*-indol-3-yl)-propionaldehyde (561.7 mg, 3.00 mmol) for 4 h to provide the title compound (83% NMR yield, 98% ee). IR (film) 3401, 3266, 3049, 2928 1601, 1546, 1494, 1473, 1424, 1376, 1328, 1249, 1155, 1127, 1065, 1028, 1012, 898.6, 740.1, 693.9, 565.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.70 (dd, *J* = 0.8, 8.0, Hz, 1H, ArH), 7.40- 6.96 (m, 9H, Ar), 4.36- 4.27 (m, 1H, CHON), 3.93 (dd, *J* = 2.7, 12.0 Hz, 1H, C**H**$_2$OH), 3.83 (dd, *J* = 5.8, 12.0 Hz, 1H, C**H**$_2$OH), 3.79 (s, 3H, CH_3), 3.28 (dd, *J* = 5.8, 14.6 Hz, 1H, C**H**$_2$Ar), 3.07 (dd, *J* = 8.0, 14.6 Hz, 1H, C**H**$_2$Ar); ^{13}C NMR (75 MHz, $CDCl_3$) □ 148.5, 136.9, 128.9, 127.9, 127.5, 122.3, 121.6, 118.9, 118.9, 114.7, 110.1, 109.2, 84.3, 64.3, 32.5, 25.6; HRMS (CI) exact mass calcd for ($C_{18}H_{20}N_2O_2$) requires *m/z* 367.2543, found *m/z* 367.2549. [□]$_D$ = + 25.7 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (15% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 25.6 min and (*R*) isomer t_r = 32.5 min.

(*R*)-*O*-(2-Dibenzylamino-1-methyl-ethyl)-*N*-phenyl-hydroxylamine (equation 3). To a 2-dram vial equipped with a magnetic stir bar and charged with L-proline was added chloroform (500 μL) and the suspension cooled to 4 °C. After 10 minutes, nitrosobenzene (107.1 mg, 1 mmol) was added in one portion, at which time the solution became green. To the green heterogeneous solution was added propionaldehyde (216 μL, 3 mmol) in one portion. The resulting solution was stirred at 4 °C until the reaction was determined to be complete by TLC and the disappearance of the green color in solution, resulting in a final yellow homogeneous solution (2 h). The reaction mixture was then concentrated and transferred using CH_2Cl_2 (2 mL) to a vial at 0 °C containing dibenzylamine (385 μL, 2.0 mmol) and sodium triacetoxyborohydride (424 mg, 2.0 mmol) in CH_2Cl_2 (6 mL). After stirring at 0 °C for 6 h, the resulting solution was treated with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was then purified by silica gel chromatography (10% EtOAc/ hexanes) and the fractions concentrated *in vacuo* to provide the title compound as a yellow oil (267.2 mg, 71% yield, 96% ee). IR (film) 3383, 3048, 3027, 2971, 2930, 2799, 1602, 1494, 1452, 1372, 1334, 1307, 1243, 1121, 1077, 1059, 1028, 977.3, 892.5, 864.3, 737.3, 697.5, 484.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58- 6.97 (m, 16H, ArH, NH), 4.32- 4.18 (m, 1H, CH), 3.85 (d, J = 13.4 Hz, 2H, ($CH_2Ar)_2$), 3.72 (d, J = 13.4 Hz, 2H, ($CH_2Ar)_2$), 2.94 (dd, J = 7.0, 13.5 Hz, 1H, CH_2CH), 2.61 (dd, J = 4.7, 13.5 Hz, 1H, CH_2CH), 1.35 (s, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 139.8, 129.4, 129.2, 129.1, 128.8, 128.7, 128.5, 127.4, 121.7, 114.4, 59.6, 58.6, 18.1; HRMS (CI) exact mass calcd for ($C_{23}H_{26}N_2O$) requires *m/z* 347.2123, found *m/z* 347.2126. $[\alpha]_D$ = + 29.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio

was determined by HPLC using a Chiracel AD and AD guard column (5.0% isopropanol / hexanes, 1 mL/min); (*S*) isomer t_r = 14.6 min and (*R*) isomer t_r = 25.0 min.

Stereochemical Analysis

Procedure for $CuSO_4$ N–O bond cleavage: To a 2-dram vial equipped with a magnetic stir bar and charged with the appropriate oxy–aniline adduct was added methanol (3 mL) and the solution cooled to 4 °C. After 10 minutes, copper sulfate (30 mmol %) was added in one portion. The resulting solution was then stirred at 4 °C until the reaction was determined to be complete by TLC analysis. The reaction was then treated with saturated aqueous sodium chloride, extracted with EtOAc (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (50% EtOAc / hexanes) and fractions concentrated *in vacuo* to provide the title compounds.

(*R*)-Hexane-1,2-diol. Prepared according to the procedure for $CuSO_4$ N–O bond cleavage from (*R*)-2-(*N*-phenyl-aminooxy)-hexan-1-ol (207 mg, 1 mmol) for 12 h to provide the title compound as a colorless oil (56.9 mg, 48% yield). The title compound was identical in all respects to the known literature compound.[39] $[\alpha]_D$ = + 15.7 (c = 1.0, EtOH); reported rotation for (*S*)-hexane-1,2-diol $[\alpha]_D$ = – 22.1 (c = 1.0, EtOH).[39]

(*R*)-3-Phenyl-propane-1,2-diol. Prepared according to the procedure for $CuSO_4$ N–O bond cleavage from (*R*)-3-phenyl-2-(*N*-phenyl-aminooxy)-propan-1-ol (243.3 mg, 1 mmol) for 12 h to provide the title compound as a colorless oil (80.2 mg, 68% yield).

The title compound was identical in all respects to the known literature compound.[39] $[\alpha]_D$ = +25.5 (c = 1.0, EtOH); reported rotation for (*S*)-3-Phenyl-propane-1,2-diol $[\alpha]_D$ = –29.5 (c = 1.0, EtOH).[39]

(*R*)-1-Phenyl-ethane-1,2-diol. Prepared according to the procedure for $CuSO_4$ N–O bond cleavage from (*R*)-2-phenyl-2-(*N*-phenyl-aminooxy)-ethanol (230 mg, 1 mmol) for 3 h to provide the title compound as a colorless oil (71.9 mg, 52% yield). The title compound was identical in all respects to the known literature compound.[40] $[\alpha]_D$ = +25.5 (c = 1.0, EtOH); reported rotation for (*S*)-1-Phenyl-ethane-1,2-diol $[\alpha]_D$ = –24.7 (c = 1.0, EtOH).[40]

Procedure for Linearity Experiment

To minimize errors from weighing of the proline antipodes, a stock solution of $CHCl_3$ (9.5 mL) and MeOH (0.5 mL) containing the appropriate ratios of L-proline and D-proline (total of 115.1mg, 1 mmol) was prepared. To a 2-dram vial equipped with a magnetic stir bar was added the stock solution (1.0 mL). Nitrosobenzene (53.8 mg, 0.5 mmol) was added in one portion, at which time the solution became teal. To this teal homogeneous solution was then added propionaldehyde (108 μL, 1.5 mmol) in one portion. The resulting solution was then stirred until the reaction was determined to be complete by TLC and the disappearance of teal color in solution, resulting in a final orange solution. The reaction mixture was then transferred to an ethanol suspension of $NaBH_4$ at 0 °C. After 20 minutes, the reaction was treated with saturated aqueous $NaHCO_3$, extracted with dichloromethane (3 x 30 mL), dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. The enantiomeric ratio was determined by HPLC using a Chiracel AD and AD guard column (10% ethanol / hexanes, 1 mL/min); (*S*) isomer t_r = 34.4 min and (*R*) isomer t_r = 40.0 min.

Kinetics Experiment

To a 2-dram vial equipped with a magnetic stir bar and charged with L-proline (1.2 mg, 0.01 mmol) was added $CDCl_3$ (3.8 mL), MeOH (0.2 mL), and tetramethylsilane (1 drop). The suspension was cooled for 10 minutes before nitrosobenzene (53.8 mg, 0.5 mmol) was added in one portion, at which time the solution became teal. To this teal heterogeneous solution, propionaldehyde (216 □L, 1.5 mmol) was added in one portion, rapidly mixed, and 750 □L of the solution was transferred to a NMR tube. The rate of the reaction was observed by measuring the area of propionaldehyde formyl proton relative to the standard tetramethylsilane.

Visual Comparison Experiment

Heterogeneous conditions: To a 2-dram vial equipped with a magnetic stir bar and charged with L-proline (5.8 mg, 0.025 mmol) was added chloroform (500 μL). Nitrosobenzene (53.8 mg, 0.5 mmol) was added in one portion, at which time the solution became teal. To this teal *heterogeneous* solution was then added the propionaldehyde (108 □L1.5 mmol) in one portion. The resulting solution was then followed visually by digital photography.

Homogeneous conditions: To a 2-dram vial equipped with a magnetic stir bar and charged with L-proline (5.8 mg, 0.025 mmol) was added chloroform (475 μL) and MeOH (25 μL). Nitrosobenzene (53.8 mg, 0.5 mmol) was added in one portion, at which time the solution became teal. To this teal *homogeneous* solution was then added the propionaldehyde (108 □L1.5 mmol) in one portion. The resulting solution was then followed visually by digital photography.

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Chapter 5

Enantioselective Organocatalytic α-Chlorination of Aldehydes

I. Introduction

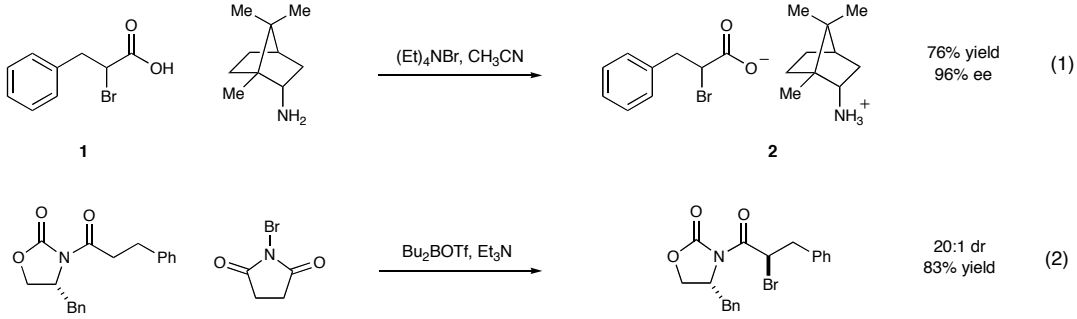
The Utility of Enantioenriched Halogen Stereocenters

The enantioselective construction of carbon–halogen bonds has become an important objective in the fields of medicinal and organic chemistry.[1-7] Within the realm of drug design, the stereospecific replacement of C–H or C–Me bonds with fluorine or chlorine atoms can often endow metabolic stability without loss in substrate binding affinity.[8] Meanwhile, as a stereodefined electrophile, the α-halocarbonyl substructure represents a versatile linchpin for organic fragment coupling and the stereocontrolled construction of C–C, C–N, C–S or C–O bonds.[9,10]

Asymmetric Construction of Halogen Stereocenters

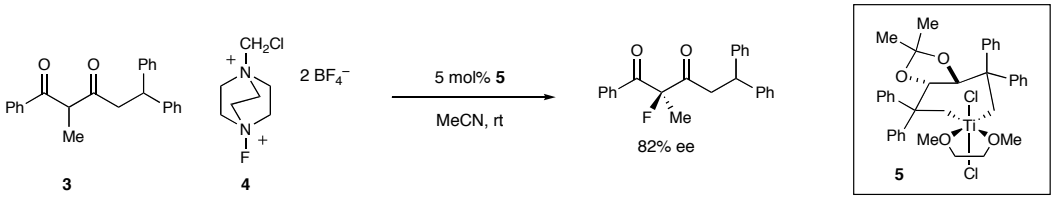
With the wide utility that asymmetric halogen stereocenters provide, it is surprising that there are relatively few procedures for accessing them in enantioenriched form. Classical resolution to form diastereomeric salts has been the most widely used methodology, but requires acidic or basic functionality while only providing a maximum yield of 50% due to loss of the unwanted enantiomer. Recently, dynamic kinetic resolution procedures to access α-bromoacids have been reported, in which the α-bromoacid **1** undergoes continual epimerization while only one of the antipodes is selectively crystallized to afford a single diastereomeric salt **2** (eq 1).[11] Diastereoselective

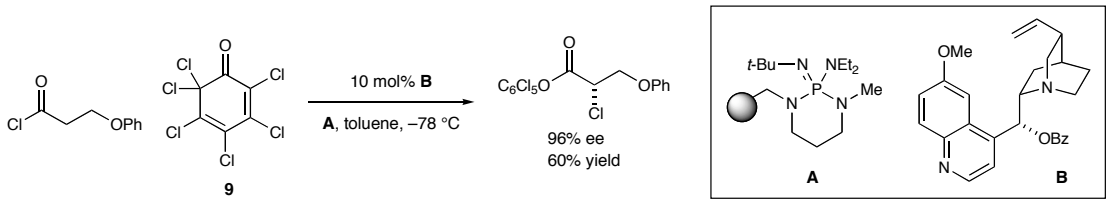
methodology using Lewis acid activation in conjunction with chiral auxiliaries has been developed by Evans to perform asymmetric α-brominations (eq 2).[12]



Enantioselective Catalytic Construction of Halogen Stereocenters

Surprisingly, there were no reports of enantioselective catalytic halogenations until Togni's manuscript in 2000[7] in which the chiral titanium catalyst **5** and fluorinating source **4** were used to perform the enantioselective fluorination of the 1,3-dicarbonyl **3** (eq 3). Since this report, several other procedures for the halogenation of 1,3-dicarbonyl have appeared, but due to epimerization, these methodologies are restricted to the formation of fully substituted stereocenters.[2,3,6,7] Elegant work by Leckta provided the first general procedure for α-halogenation of carbonyls.[1,4,5] This organocatalytic process utilized a tertiary amine catalyst to activate acid chlorides toward nucleophilic attack of the chlorinating agent **9** to provide α-haloesters in moderate levels of chemical yield and high levels of enantioselectivity (eq 4).

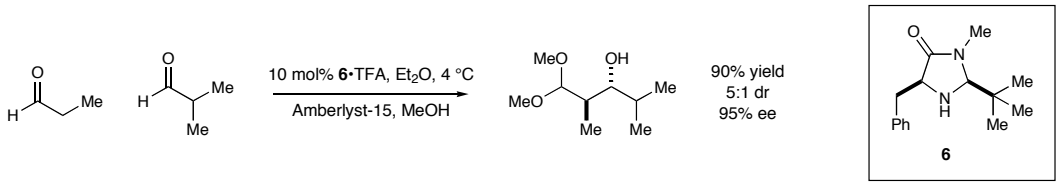




(4)

Imidazolidinone Catalyzed Enamine Activation

Elegant work by Ian Mangion[13] in our group displayed that the imidazolidinone catalysts will participate in HOMO-raising enamine activation with aldehydes. The secondary amine **6** catalyzes the heterodimerization of aldehydes, producing aldol products in high levels of diastereo- and enantioselectivity (eq 5).

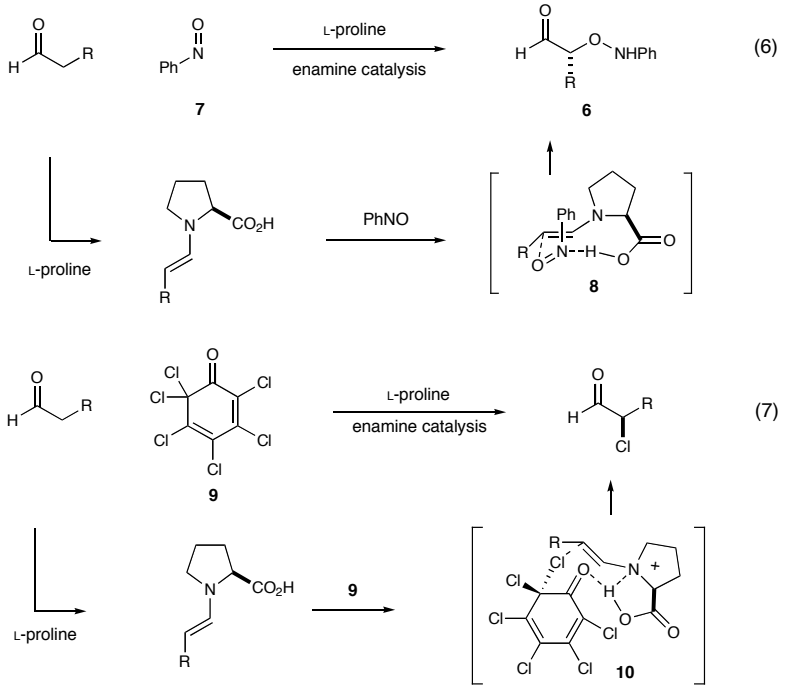


(5)

II. Results and Discussion

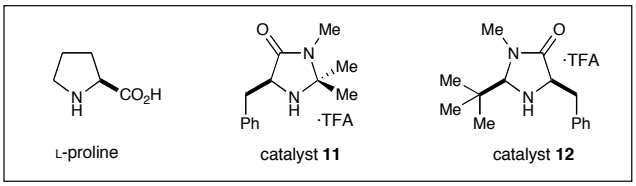
First Generation Enantioselective Catalytic α-Chlorination

Chapter 4 describes the enantioselective α-oxidation of aldehydes,[14,15] where in the enantioselective step was proposed to involve a proton-mediated cyclic transition state **8** that enforces nitrosobenzene (**7**) activation in the asymmetric environment of a π-rich enamine (eq 6). Intrigued by the possibility that such a mechanistic scenario might be expanded to encompass electrophilic forms of chlorine, we identified *N*-chlorosuccinimide (NCS) and the perchlorinated quinone **9** as reagents that might engage in an analogous transition state **10** via carbonyl–proton association and concomitant chlorine activation (eq 7).



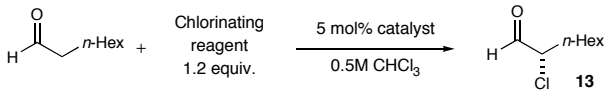
As revealed in Table 1, exposure of octanal to NCS or quinone **9** in the presence of L-proline resulted in a facile but non-selective aldehyde chlorination (Table 1, entries 1 and 4). We hypothesized that the cyclic transition state **10**, necessary for high level of enantioselectivity, was highly strained and that the reaction may proceed through transition state **14** utilizing two molecules of proline affording low levels of enantioselectivity (Figure 2). Changing catalyst structure to an imidazolidinone architecture which does not require that the acid cocatalyst be tethered to the catalyst framework (Figure 2, **15**) was initially less than fruitful with the imidazolidinone **12** (Figure 1) (Table 1, entry 3 and 7, 10% and 42% ee). However, a dramatic increase in enantioselectivity was achieved using quinone **9** in the presence of amine catalyst **11** to access (*S*)-2-chloro-octanal (**13**) in 92% ee (Table 1, entry 6).

Figure 1. Secondary amine catalyst architecture



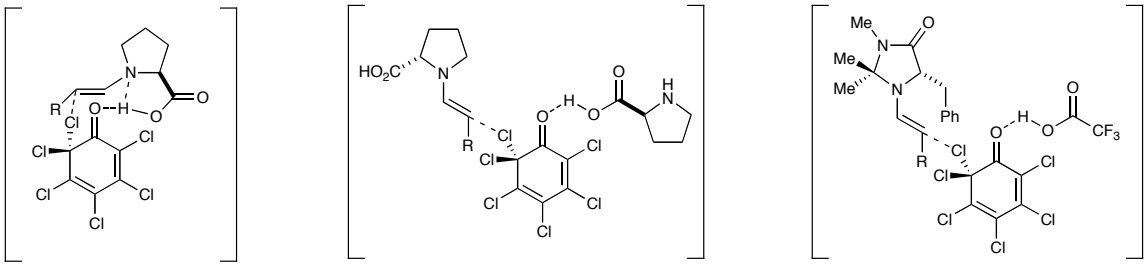
L-proline catalyst **11** catalyst **12**

Table 1. Effect of catalyst and chlorinating reagent on α-chlorination



entry	catalyst	reagent	temp. (°C)	time (h)	% conversion[a]	% ee[b]
1	L-proline	NCS	4	6	99	2
2	**11**	NCS	4	6	20	19
3	**12**	NCS	4	6	60	10
4	L-proline	**9**	4	12	44	2
5	L-proline	**9**	–30	30	NR	NA
6	**11**	**9**	–30	8	91	92
7	**12**	**9**	–30	6	78	42

Figure 2. Proposed transition states for organocatalyzed α-chlorination



10 strained cyclic transition structure

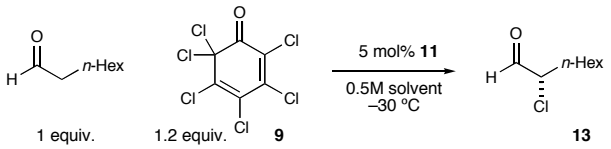
14 180° approach small steric bias

15 180° approach to Cl–C σ*

A survey of reaction media for this organocatalytic chlorination revealed that a variety of solvents may be employed without significant loss in enantiocontrol (Table 2). Surprisingly, the use of acetone provided optimal selectivity, reaction rate, and chemical yield, without halogenation of the bulk medium (entry 6, 93% conversion, 92% ee).

Moreover, product epimerization, formation of α,α-dichlorooctanal or octanal aldol dimerization[13,16] were comprehensively suppressed using these conditions. The superior levels of asymmetric induction and efficiency exhibited by amine salt **11** in acetone at –30 °C to afford (*S*)-2-chloro-octanal (**13**) in 92% ee prompted us to select these catalytic conditions for further exploration.

Table 2. Effect of solvent on the organocatalyzed α-chlorination

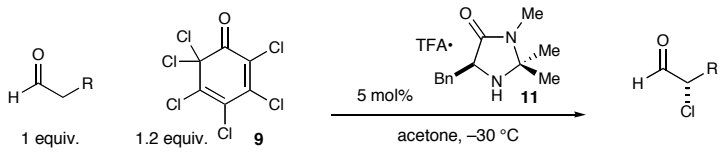


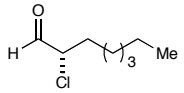
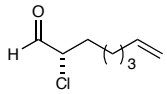
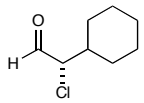
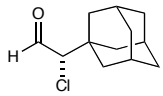
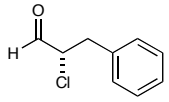
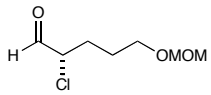
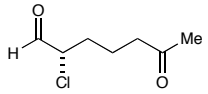
1 equiv. 1.2 equiv. **9** **13**

entry	solvent	time (h)	% conversion	% ee
1	EtOAc	12	93	87
2	THF	18	56	89
3	toluene	18	83	89
4	CH_3CN	8	65	92
5	$CHCl_3$	8	91	92
6	acetone	7	93	92

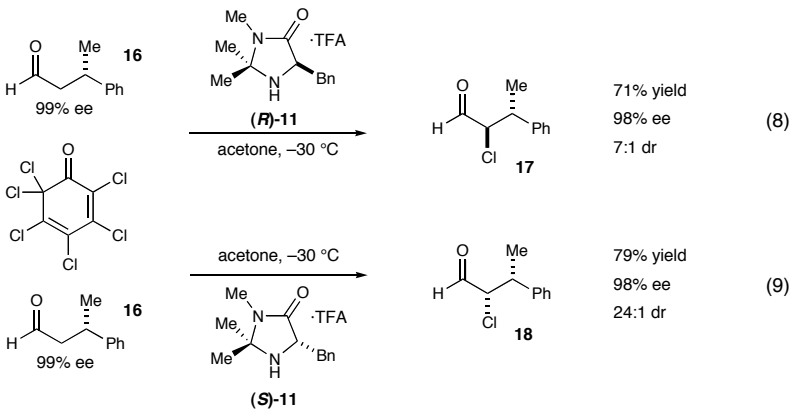
Experiments that probe the scope of the aldehyde substrate are summarized in Table 3. Considerable variation in the steric demand of the aldehyde component (entries 1,3-5, R = *n*-Hex, *c*-Hex, adamantyl, Bn) is possible without loss in efficiency or enantiocontrol (71–85% yield, 92 to 94% ee). Moreover, these mild catalytic conditions are tolerant of acid sensitive functionality such as acetals (Table 3, entry 6). It is important to note that these α-chloroaldehydes are typically configurationally stable to pH neutral silica purification.[17] Indeed, only the α-chloro-hydrocinnamaldehyde adduct was found to significantly diminish in optical purity upon isolation (entry 5, crude 92% ee, isolated 80% ee).

Table 3. Enantioselective α-chlorination: substrate scope



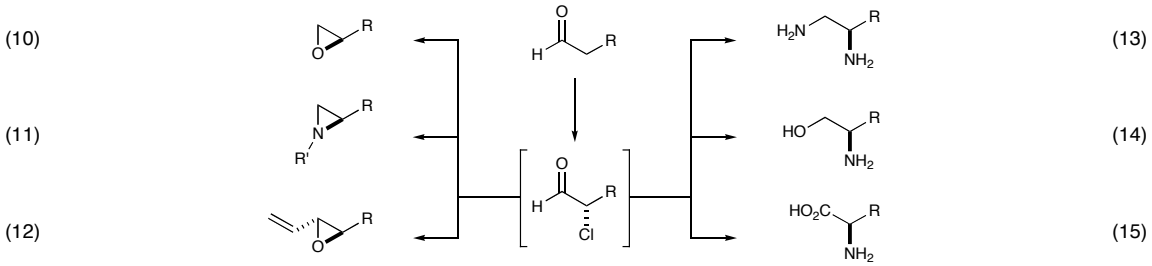
entry	product	time (h)	% ee crude	% yield	% ee isolated
1		6	95	71	92
2		8	93	75	91
3		8	94	87	94
4		24	NA	85	95
5		6	92	92	80
6		12	93	94	93
7		12	91	78	87

We next examined the ability of catalyst **11** to override the inherent bias of resident stereochemistry in the chlorination of enantiopure α-chiral aldehydes. As shown in equations 8 and 9, exposure of enantiopure (*S*)-3-phenyl-butyraldehyde (**16**) to catalyst antipode (*R*)-**11** results in the diastereoselective production of the *syn* α,β-disubstituted isomer **17**, while the catalyst antipode (*S*)-**11** affords the corresponding *anti* adduct **18** with high fidelity. These transformations clearly demonstrate the synthetic advantages of catalyst-enforced induction versus substrate directed stereocontrol.



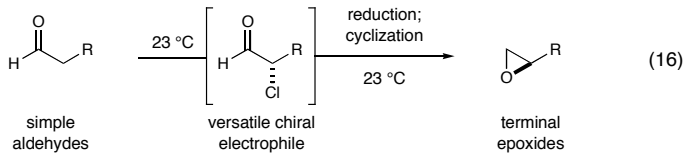
Development of a Room Temperature Enantioselective α-Chlorination

The field of asymmetric catalysis has developed rapidly in the last thirty years. Highly enantioselective catalysts have been developed for hydrogenation, cyclizations, and carbon-carbon bond forming reactions.[18] However, there remain a variety of versatile functionalities that cannot be achieved directly in high levels of enantiomeric excess. We envisioned using the α-chlorination of aldehydes as a point of diversity for the construction of asymmetric functionalities directly from aldehydes, utilizing the versatile nature of α-chloroaldehydes to react in a stereo-defined manner with a variety of nucleophiles (eq 10-15).



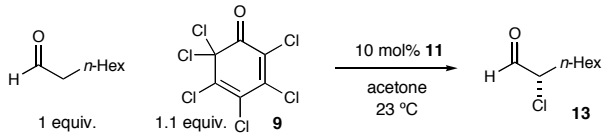
As a first step toward this broader goal, we embarked on the enantioselective synthesis of terminal epoxides directly from simple aldeydes (eq 10). Enantiopure epoxides are abundant in natural isolates and highly versatile as functional intermediates,

which has simulated the development of many highly successful organometallic and organocatalytic processeses for the synthesis. However, there are no methods for enantioselective catalytic construction of terminal epoxides. We imagined that α-chlorination of simple aldehydes, followed by reduction and oxirane formation would provide highly enantioenriched terminal epoxides (eq 16). To provide a truly operationally simple procedure, it would be optimal for the process to occur entirely at ambient conditions. The reduction and cyclization conditions necessary for the single operation terminal epoxide formation depicted in equation 16 can be achieved at room temperature, but the asymmetric α-chlorination required –30 °C.



(16)

Table 4. Ambient temperature α-chlorination utilizing catalyst **11**

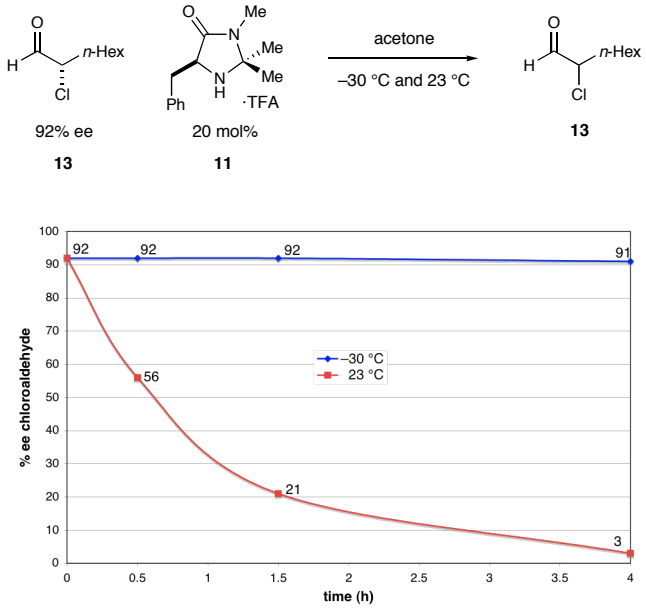


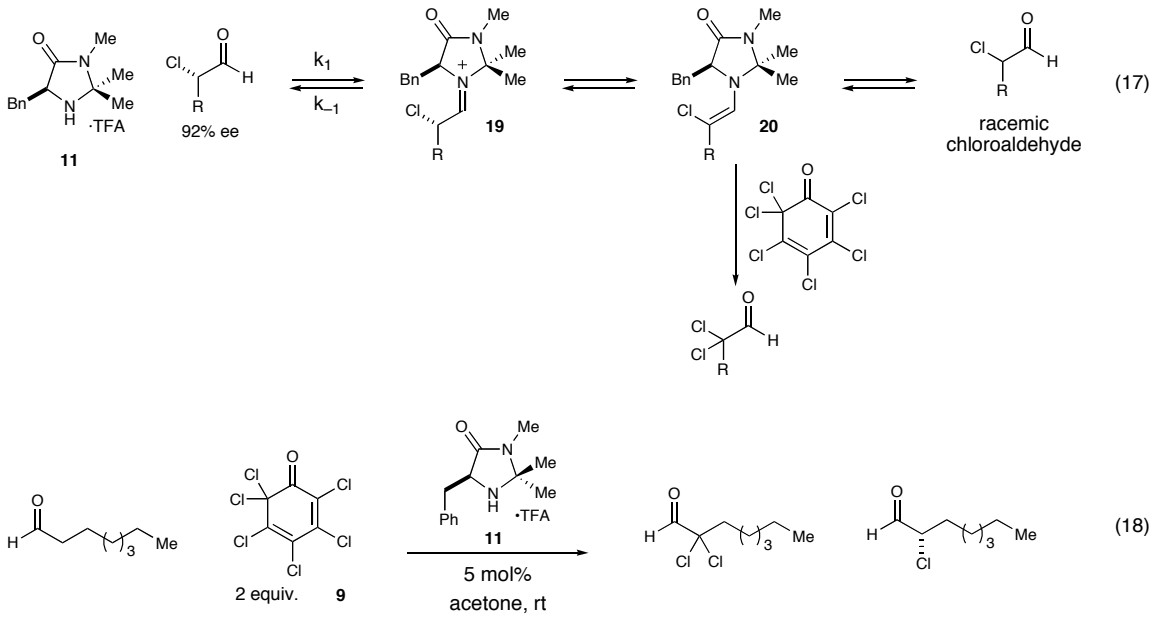
entry	minutes	% conversion	% ee
1	3	97	80
2	6	97	76
3	18	97	72
4	36	94	65
5	90	90	49
6	240	85	28

To further understand the temperature constraints, the enantioselective α-chlorination of aldehydes was investigated at 23 °C. This provided lower levels of enantioselectivity (Table 4, entry 1, 97% conversion, 80% ee), compared to the enantioselectivity at –30 °C (Table 1, entry 1, 94% ee). Both the chemical yield and

enantiomeric excess of (*S*)-2-chlorooctanal (**13**) also decreased over time upon further exposure to the reaction conditions (Table 4, entries 1-6, 80–28% ee). Moreover, when 92% ee (*S*)-2-chlorooctanal (**13**) was exposed to catalyst **11** at –30 °C and 23 °C (Figure 3), excellent retention of enantioselectivity is observed at –30 °C while epimerization occurs at 23 °C. We postulated that epimerization and loss of product arose from the condensation of the α-chloroaldehyde product with catalyst **11** to form the iminium ion **19** that undergoes epimerization or a second chlorination by way of chloroenamine **20** (eq 17). In fact, when 2 equivalents of the quinone **9** were used at room temperature, a mixture of mono- and dichlorination was observed (eq 18).

Figure 3. Exposure of (*S*)-2-chlorooctanal (**13**) to catalyst **11**

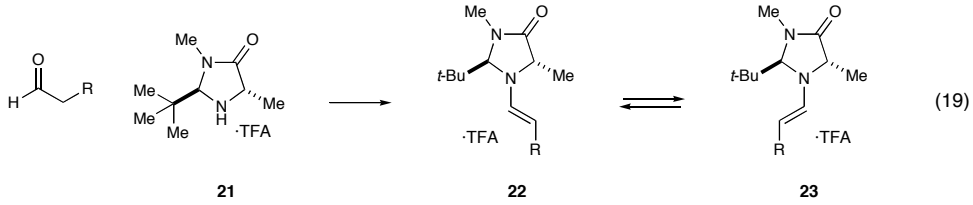




Second Generation Enantioselective Catalytic α-Chloriantion

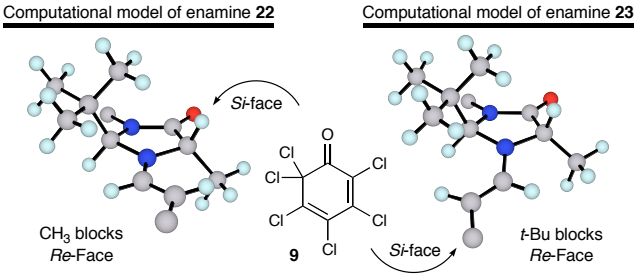
Catalyst **11** required modification of the reaction temperature to increase enantioselection and decrease the rate of catalyst condensation with the α-chloroaldehyde product (Table 3, entry 1, –30 °C, 95% ee, 6 h). The incompatibility of the catalyst **11** for the reduction and cyclization conditions necessary for epoxide formation required that a new α-chlorination catalyst be developed that would provide increased enantiomeric excess at ambient temperature. To provide greater transition state organization, pseudo C_2 symmetry was used as a design criteria for the development of catalyst **21** to improve enantioselection at 23 °C. Condensation of catalyst **21** with an aldehyde generates enamine rotomers **22** and **23** (eq 19), which are approached from the *Si*-face by the chlorinating reagent **9**, due to the presence of the eclipsing *tert*-butyl or methyl group blocking the *Re*-face of enamine rotomers **22** and **23**, respectively (Scheme 1). Additionally, the increased steric bulk proximal to the nucleophilic nitrogen of catalyst

21 should decrease the rate of epimerization by disfavoring catalyst condensation with the α-chloroaldehyde product (Scheme 2).

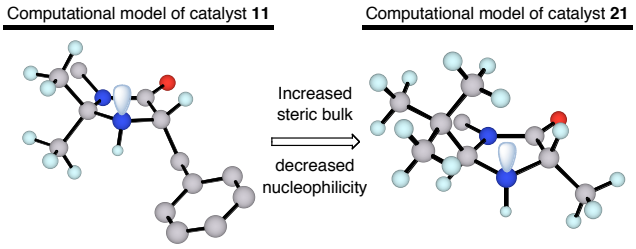


(19)

Scheme 1. Pseudo C_2 symmetry



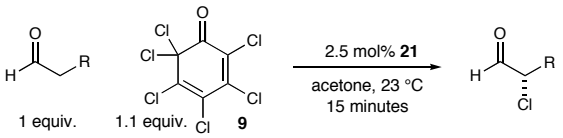
Scheme 2. Increased catalyst steric bulk leads to product configurational stability



Gratifyingly, when catalyst **21** was utilized for the asymmetric α-chlorination at ambient temperature, it provided rapid, yet selective α-chlorination of octanal (Table 5, entry 1, 15 min., 96% yield, 97% ee). Experiments to probe the scope of the aldehyde substrate were conducted under the optimized reaction conditions (Table 5). Considerable variation in the steric demand of the aldehyde component (entries 1, 3, 5, R = *n*-Hex, *c*-Hex, and benzyl) was possible without loss in efficiency or enantiocontrol

(83–96% yield, 92–97% ee). Furthermore, the mild reaction conditions proved tolerant to olefins and acid sensitive functionalities (entry 2, 5, 96–98% yield, 94% ee). Proper tuning of the sterics proximal to the nucleophilic imidazolidinone nitrogen dramatically increased configurational stability of (*S*)-2-chlorooctanal (**13**) upon exposure to catalyst **21**. Complete retention of enantiomeric excess was observed at 4 °C and good configurational stability was achieved at 23 °C (Figure 4).

Table 5. Enantioselective α-chlorination: substrate scope



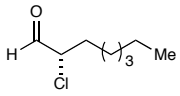
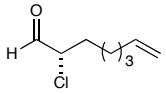
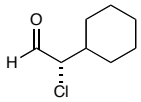
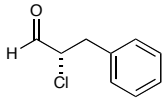
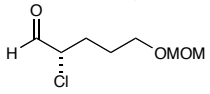
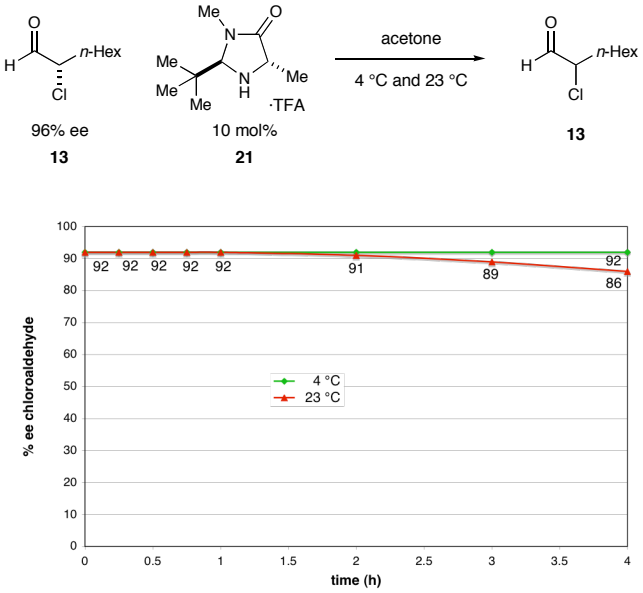
entry	product	% yield	% ee
1		96	97
2		98	94
3		83	92
4		95	90
5		96	94

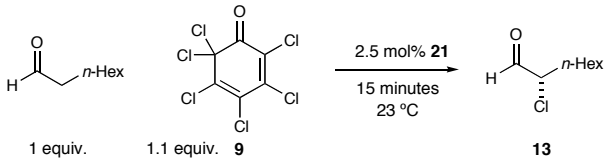
Figure 4. Exposure of (*S*)-2-chlorooctanal (**13**) to catalyst **21**



Enantioselective Single Operation Construction of Terminal Epoxides

Development of catalyst **21** provided a highly efficient and enantioselective process to generate α-chloroaldehydes that should be compatible with reduction and cyclization conditions to construct asymmetric terminal epoxides, due to the ability of catalyst **21** to operate at ambient conditions. Although catalyst **21** provided highly enantioselective α-chlorination of octanal in a range of solvents (Table 6, 92–97% ee), tetrahydrofuran (THF) was selected to pursue further studies due to its compatibility with the reduction and cyclization conditions necessary for oxirane formation (eq 16).

Table 6. Effect of solvent on the organocatalyzed α-chlorination

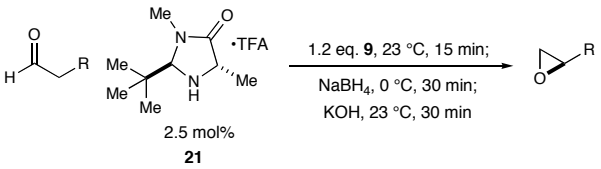


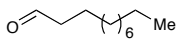
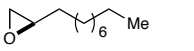
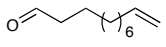
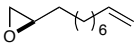
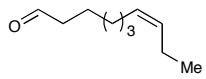
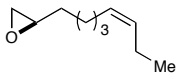
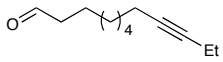
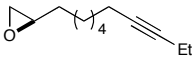
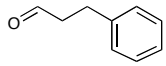
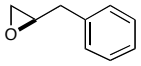
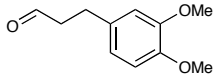
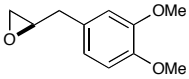
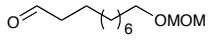
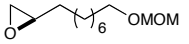
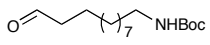
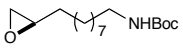
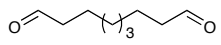
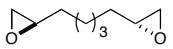
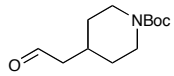
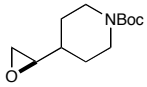
1 equiv. 1.1 equiv. **9** **13**

entry	solvent	% conversion	% ee
1	acetone	96	97
2	THF	96	96
3	toluene	88	96
4	MeCN	63	93
5	CH_2Cl_2	68	92
6	EtOAc	90	95

The conversion of simple aldehydes to terminal epoxides was achieved by Teresa Beeson utilizing only 2.5 mol% of amine catalyst **21** in only 75 minutes (Table 7). Enantioselective 15 minute α-chlorination of the aldehyde was followed by a 30 minute $NaBH_4$ aldehyde reduction and a 30 minute oxirane formation promoted by KOH, providing terminal epoxides in high levels of enantioselectivity (Table 7, 92–99% ee). These mild reaction conditions tolerate electron-rich π-systems that are typically prone to oxidation under many epoxidation conditions (entries 2–6, 76–96% yield, 92–95% ee). Acid sensitive functionalities such as acetals and *tert*-butylcarbamates are tolerated, affording the corresponding terminal epoxides in good levels of reaction efficiency and high levels of enantiomeric excess (entries 7, 8, 10, 75–86% yield, 93–96% ee).

Table 7. Enantioselective α-chlorination: substrate scope



entry	substrate	product	% yield	% ee
1			83	94
2			82	92
3			78	94
4			76	95
5			77	93
6			96	94
7			75	93
8			83	95
9			81	>99
10			86	96

III. Conclusion

In summary, we have described the first direct, enantioselective α-chlorination of aldehydes.[19] Importantly, the chlorinated quinone **9** and both enantiomers of catalyst **11** are bench stable and commercially available. Furthermore, this methodology was utilized to perform the first direct catalytic and enantioselective construction of terminal

epoxides. The design and development of a new catalyst **21** for the room temperature asymmetric α-chlorination of aldehydes was necessary to achieve high levels of enantioselectivity and reaction efficiency. Finally, it should be noted that the imidazolidinone scaffold has revealed itself to be a broadly useful catalyst for enantioselective synthesis within the realms of both iminium activation,[20-30] and now enamine catalysis.

IV. Experimental Section

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[31] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still.[32] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain. Gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 Series gas chromatography equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex -TA (30 m 0.25 mm) column.

Procedures

General Procedure: A 10 mL round-bottom flask equipped with a magnetic stir bar and charged with (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (16.6 mg, 0.05 mmol) and acetone (2 mL) was allowed to cool to –30 °C for five minutes prior to addition of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (361 mg, 1.2 mmol). The aldehyde substrate (1 mmol) was added to the yellow homogenous solution. The resulting mixture was stirred at –30 °C until the reaction was determined to be complete by GLC, at which time the mixture was a pale yellow heterogeneous solution. The reaction was then eluted with Et_2O and passed through Iatrobeads (8 g), and the resulting organics were carefully concentrated *in vacuo* (using an ice bath). The resulting residue was purified by Iatrobeads chromatography (solvents noted) and organics carefully concentrated *in vacuo* with an ice bath to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

5-Methoxymethoxy-pentanal: To a flask containing 1,5-pentanediol (34 mL, 330 mmol) and NEt_3 (13.7 mL, 99 mmol) in CH_2Cl_2 (150 mL) was slowly added chloromethyl methyl ether (5.0 ml, 65.8 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was then treated with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (2 × 100 mL), dried over Na_2SO_4, and concentrated. Iodobenzene diacetate (8.4 g, 26.2 mmol) was then added to a solution of the crude product (3.5 g, 24 mmol) and TEMPO (0.37 g, 2.4 mmol) in CH_2Cl_2 (50 mL).[33] The reaction was stirred for 12 hours and then diluted with CH_2Cl_2 (250 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (150 mL) and

extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL), dried over $NaSO_4$, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (40% Et_2O/ pentane) and the organics carefully concentrated *in vacuo* with an ice bath to provide the title compound. IR (film) 2941, 2871, 2720, 1725, 1454, 1383, 1353, 1262, 1201, 1138, 1122, 1078, 1035, 991.9, 905.0, 868.3, 814.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, 1H, *J* = 1.5 Hz, CHO), 4.58 (s, 2H, CH_2OMe), 3.51 (t, 2H, *J* = 6.5 Hz, $CH_2C\mathbf{H_2}O$), 3.33 (s, 3H, CH_3), 2.46 (td, *J* = 1.5, 7.3 Hz, 2H), 1.76- 1.54 (m, 4H, $(C\mathbf{H_2})_2CH_2CHO$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 96.4, 67.1, 55.1, 43.5, 29.1, 18.9; HRMS (CI) exact mass calculated for ($C_7H_{13}O_3$) requires *m*-1/*z* 145.0865, found *m*-1/*z* 145.0862.

(*S*)-2-Chloro-octanal (Table 3, entry 1): Prepared according to the general procedure from octylaldehyde (156 μL, 1.00 mmol) for 6 h to provide the title compound as a colorless oil (115.2 mg, 71% yield, 92% ee) after Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 3385, 2957, 2927, 2858, 1458, 1400, 1378, 1343, 1138, 1102, 1069, 879.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, 1H, *J* = 2.7 Hz CHO), 4.19 (ddd, 1H, *J* = 2.7, 5.6, 8.2 Hz, CHCl), 2.06- 1.95 (m, 1H, $ClCC\mathbf{H}_2$), 1.90- 1.79 (m, 1H, $ClCC\mathbf{H}_2$), 1.62- 1.26 (m, 8H, $(C\mathbf{H_2})_4CH_3$), 0.92 (t, *J* = 6.9 Hz, 3H, $C\mathbf{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 64.0, 32.1, 31.5, 28.6, 25.5, 22.5, 14.0; HRMS (CI) exact mass calculated for ($C_8H_{15}ClO$) requires *m*/*z* 162.0811, found *m*/*z* 167.0812. $[\alpha]_D$ = –35.47 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 75.5 min and (*S*) isomer t_r = 81.4 min.

(*S*)-2-Chloro-7-octenal (Table 3, entry 2): Prepared according to the general procedure from oct-7-enal (126 mg, 1.00 mmol) for 8 h to provide title compound as a colorless oil (114 mg, 76% yield, 92% ee) after Iatrobeads chromatography (2% Et_2O/ pentane). IR (film) 3853, 3676, 3406, 2970, 2928, 2855, 2357, 2325, 1279, 1102, 1076, 905.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.45 (d, 1H, *J* = 2.2 Hz, CHO), 5.83-5.69 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 4.97 (dd, 2H, *J* = 1.7, 10.1 Hz, $CH=C\mathbf{H_2}$), 4.13 (ddd, 1H, *J* = 2.2, 6.7, 7.1 Hz, CHCl), 2.09-1.99 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 2.02-1.93 (m, 1H, $ClCC\mathbf{H}_2$), 1.88-1.76 (m, 1H, $ClCC\mathbf{H}_2$) 1.62-1.38 (m, 4H, $CH_2(C\mathbf{H_2})_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 195.5, 138.4, 115.1, 64.1, 33.5, 32.1, 28.4, 25.2; HRMS (CI) exact mass calculated for ($C_8H_{13}ClO$) requires *m/z* [M-Cl] =127.0759, found *m/z* 127.0759. $[]_D$ = –40.59 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex -TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 89.3 min and (*S*) isomer t_r = 91.4 min.

(*S*)-Chloro-cyclohexyl-acetaldehyde (Table 3, entry 3): Prepared according to the general procedure from cyclohexyl-acetaldehyde[33] (138 μL, 1.00 mmol) for 8 h to provide the title compound as a colorless oil (139.8 mg, 87% yield, 94% ee) after Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 3374, 2930, 2855, 1451, 1378, 1112, 1080, 890.3, 733.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.50 (d, 1H, *J* = 3.5 Hz, CHO), 4.00 (dd, 1H, *J* = 3.5, 6.4 Hz, CHCl), 2.07- 1.92 (m, 1H, $ClCC\mathbf{H}$), 1.90- 1.66 (m, 4H), 1.43- 1.11 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 195.8, 69.4, 40.2, 29.7, 28.3, 25.9, 25.8, 25.6; HRMS (CI) exact mass calculated for ($C_7H_{12}Cl$) requires *m/z* 131.0628,

found *m/z* 131.0626. $[\alpha]_D$ = –6.01 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); (*R*) isomer t_r = 101.3 min and (*S*) isomer t_r = 111.0 min.

(*S*)-Chloro-tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde (Table 3, entry 4): Prepared according to the general procedure from tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde[34] (174 μL, 1.00 mmol) at –40 °C using (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (66.4 mg, 0.2 mmol) for 24 h to provide the title compound as a colorless oil (136.5 mg, 85% yield, 95% ee). The excess 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one was consumed by addition of propionaldehyde (29 μL, 0.40 mmol). The reaction was quenched by filtration through Iatrobeads (8 g) eluting with Et_2O and concentrated *in vacuo*. The resulting residue was purified by Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 2905, 2851, 1730, 1456, 1345, 1106, 1064, 1004, 976.2, 762.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, 1H, *J* = 4.8 Hz, CHO), 3.70 (d, 1H, *J* = 4.8 Hz, CHCl), 2.10- 2.02 (m, 3H), 1.81-1.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 73.8, 38.8, 37.1, 36.5, 28.0; HRMS (CI) exact mass calculated for ($C_{12}H_{17}ClO$) requires *m/z* 212.0968, found *m/z* 212.0970. $[\alpha]_D$ = +30.02 (c = 1.0, $CHCl_3$). Reduction of the title compound to the corresponding alcohol and cyclization with aqueous 50% KOH provided the epoxide 2-tricyclo[3.3.1.1^{0,0}]dec-1-yl-oxirane, which matched literature data.[35] The enantiomeric ratio of the epoxide was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (100 °C isotherm, 1 mL/min); (*S*) isomer t_r = 49.3 min and (*R*) isomer t_r = 51.6 min.

(*S*)-2-Chloro-hydrocinnamaldehyde (Table 3, entry 5): Prepared according to the general procedure from hydrocinnamaldehyde (62 mg, 0.50 mmol) in d_6-acetone for 6 h. To a reaction flask was added benzyl methyl ether (61 mg, 0.50 mmol). The title compound was provided (92% NMR yield, 92% ee), then isolated as a colorless oil (80% ee) after Iatrobeads chromatography (2% Et_2O/ pentane). The title compound was identical in all respects to the known literature compound with regards to NMR and HRMS data.[36] IR (film) 3511, 2360, 2341, 1717, 1653, 1540, 1417, 1377, 1277, 1191, 1111, 767.7, 701.6 cm^{-1}; $[\alpha]_D$ = –8.84 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); (*R*) isomer t_r = 234.3 min and (*S*) isomer t_r = 245.4 min.

(*S*)-2-Chloro-5-methoxymethoxy-pentanal (Table 3, entry 6): Prepared according to the general procedure from 5-methoxymethoxy-pentanal (170 μL, 1.00 mmol) at –40 °C for 12 h to provide the title compound as a colorless oil (139.8 mg, 94% yield, 93% ee) after Iatrobeads chromatography (40% Et_2O/ pentane). IR (film) 3401, 2932, 2885, 2826, 1736, 1445, 1386, 1346, 1149, 1110, 1040, 919.5, 775.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (d, 1H, *J* = 2.1 Hz, CHO), 4.62 (s, 2H, CH_2OMe), 4.26 (ddd, 1H, *J* = 2.1, 5.1, 8.5 Hz, CHCl), 3.59 (t, 2H, *J* = 5.8 Hz, $CH_2C\mathbf{H_2}O$), 3.37 (s, 3H, $C\mathbf{H_3}$), 2.22- 2.09 (m, 1H), 2.00- 1.68 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 96.4, 66.5, 63.7, 55.3, 29.1, 25.8; HRMS (CI) exact mass calculated for ($C_7H_{14}ClO_3$) requires *m/z* 181.0632, found *m/z* 181.0632. $[\alpha]_D$ = –12.68 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm)

column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 260.4 min and (*S*) isomer t_r = 267.5 min.

(*S*)-2-Chloro-6-oxo-heptanal (Table 3, entry 7): Prepared according to the general procedure from 6-oxo-heptanal[37] (128 mg, 1.0 mmol) for 12 h to provide title compound as a colorless oil (134 mg, 78% yield, 87% ee) after Iatrobeads chromatography (35% Et_2O/ pentane). IR (film) 3420, 2933, 2855, 2360, 1732, 1715, 1418, 1363, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.47 (d, 1H, *J* = 2.3 Hz, CHO), 4.16 (dd, 1H, *J* = 2.2, 7.2 Hz, CHCl), 2.47 (t, 2H, *J* = 7.2 CH_2CO), 2.12 (s, 3H, C**H**$_3$), 2.03-1.93 (m, 1H), 1.85-1.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 207.9, 195.1, 63.8, 42.7, 31.4, 30.1, 19.9; HRMS (CI) exact mass calculated for ($C_7H_{15}ClO2$) requires *m/z* =160.0655, found *m/z* 160.0658. [□]$_D$ = –49.93 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex □-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); (*R*) isomer t_r = 144.1 min and (*S*) isomer t_r = 149.3 min.

(*R*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 3, 17): Prepared according to the general procedure from (*S)*-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide the title compound as a colorless oil (65 mg, 71% yield, 7:1 *anti:syn*, 98% ee) after Iatrobeads chromatography (1% Et_2O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.37 (d, 1H, *J* = 3.0 Hz, CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, *J*= 3.0, 6.6 CHCl), 3.47 (qd, *J* = 6.6, 7.2 Hz, 1H, C**H**CH_3), 1.46 (d, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact

mass calculated for ($C_{10}H_{11}ClO$) requires *m/z* =182.0502, found *m/z* 182.0498. $[\alpha]_D$ = –3.86 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *anti* adduct (2*R*, 3*R*) t_r = 115.5 min, *syn* adduct (2*S*, 3*R*) t_r = 189.2 min.

(*S*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 4, 18): Prepared according to the general procedure from (*S)*-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide pure title compound as a colorless oil (72 mg, 79% yield, 24:1 *syn:anti*, 98% ee) after Iatrobeads chromatography (1% Et_2O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, 1H, *J* = 3.0 Hz CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, J = 3.0, 6.6 Hz, CHCl), 3.47 (qd, 1H, *J* = 6.6, 7.2 Hz, C**H**CH_3), 1.4 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact mass calculated for ($C_{10}H_{11}ClO$) requires *m/z* =182.0502, found *m/z* 182.0498. $[\alpha]_D$ = –2.31 (c = 1.0, $CHCl_3$). The enantiomeric and diastereomeric ratios were determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *syn* adduct (2*S*, 3*R*) t_r = 111.8, *anti* adduct (2*R*, 3*R*) t_r = 190.2 min.

(2*R*,5*S*)-2-*tert*-butyl-3,5-dimethylimidazolidin-4-one (21): Synthesized following literature procedure.[33] IR (film) 3314, 2958, 2872, 1692, 1614, 1484, 1454, 1430, 1398, 1367, 1299, 1264, 1207, 1136, 1094, 1063, 1035, 989.3, 932.5, 878.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (d, 1H, *J* = 1.6 Hz CH*t*-Bu), 3.61 (q, 1H, J = 6.9 Hz, CHMe), 2.95 (s, 3H, NCH_3), 1.29 (d, 3H, *J* = 6.9 Hz CHC**H$_3$**), 0.97 (s, 9H, $(CH_3)_3$); ^{13}C

NMR (75 MHz, $CDCl_3$) □ 176.8, 83.2, 54.2, 37.9, 31.5, 25.7, 18.5; HRMS (CI) exact mass calculated for ($C_9H_{18}N_2O$) requires *m/z* 171.1497, found *m/z* 171.1480. $[\square]_D$ = +10.68 (c = 1.0, $CHCl_3$).

Stereochemical Analysis

Procedure for Conversion to Epoxide: To a solution of (*S*)-2-chloroaldehyde (0.5 mmol) in CH_2Cl_2 (0.5 mL) and absolute ethanol (0.5 mL) was added sodium borohydride (0.5 mmol) at 0 °C. After 15 min, the resulting solution was treated with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The crude mixture was then concentrated *in vacuo*. The resultant yellow oil was then added to a round-bottom flask equipped with a magnetic stir bar. To the flask was added a solution of aqueous 50% KOH (2 mL) and allowed to stir at room temperature for 4 hours. At this time, the resulting mixture was washed with Et_2O (3 x 5 mL) before the organics were concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et_2O/ pentane).

(*R*)-Benzyl oxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-hydrocinnamaldehyde (77 mg, 0.5 mmol) to afford the title compound as a colorless oil (37 mg, 55% yield). The title compound was identical in all respects to the known literature compound. $[\square]_D$ = +10.1 (c = 1.94, EtOH); reported rotation for (*S*)-benzyl oxirane $[\square]_D$ = –17.3 (c = 1.94, EtOH).[38]

(*R*)-2-Hexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-octanal (81 mg, 0.5 mmol) to afford the title compound as a colorless oil (42 mg, 66% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D$ = +6.2 (c = 1.8, $CHCl_3$); reported rotation for (*R*)-2-hexyloxirane $[\alpha]_D$ = +7.4 (c = 4.5, $CHCl_3$).[39]

(*R*)-2-Cyclohexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-chloro-cyclohexyl-acetaldehyde (80 mg, 0.5 mmol) to afford the title compound as a colorless oil (24 mg, 38% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D$ = –2.1 (c = 0.88, $CHCl_3$); reported rotation for (*S*)-2-cyclohexyloxirane $[\alpha]_D$ = +2.1 (c = 0.88, $CHCl_3$).[40]

V. References

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Appendix 1

X-Ray Crystallographic Data

(2*S*,3*R*)-5-(*N*-Methyl-*N*-((*S*)-1-phenylethyl)amino)-2-(benzamido)-2,3-dimethylpentanoic Acid•Hydrochloride