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Thiourea/Proline Derivative-Catalyzed Synthesis of Tetrahydrofuran Derivatives: A Mechanistic View

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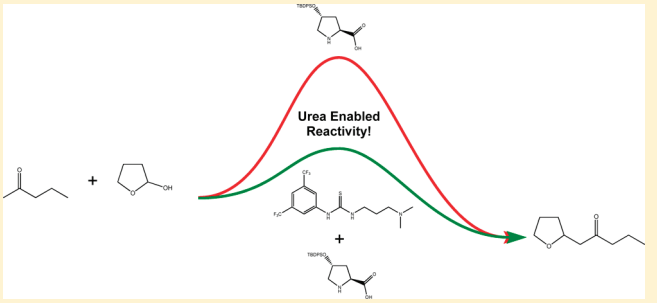
Supporting Information

ABSTRACT: A thiourea/proline derivative-catalyzed synthesis of linear α-substituted tetrahydrofuran/pyran derivatives starting with lactol substrates is presented. This study demonstrates the utility and potential complications of using (thio)urea/proline cocatalysis as each of these catalysts is necessary to provide the observed reactivity, but a time-dependent decrease in enantioselectivity is observed. New mechanistic insights into (thio)urea/proline cocatalysis are presented.



INTRODUCTION

Proline and secondary amine analogues catalyze a wide range of reactions including aldol[1] and Mannich[1b] reactions, α-aminoxylations, α-aminations, and α-halogenations,[2] to name a few.[3] As with many catalysts, proline can benefit from the addition of a cocatalyst such as an acid,[4] base,[4a,5] or hydrogen bonding species.[4,6] Of the hydrogen bonding cocatalysts, ureas[7] show some of the largest gains in catalytic activity.[8]

The role that ureas play in these systems is slowly emerging and appears to be complex and dependent on the structure of the urea.[8d,f] The first example of a urea/proline system used a diarylthiourea to accelerate an aldol reaction. The authors hypothesized that a host−guest complex was formed between proline and urea, thereby increasing the solubility of proline. ^{1}H NMR analysis indicated a downfield shift in the urea protons supporting the host−guest complex model.[8a] Furthermore, another group used UV and fluorescence data to support that a stable 1:1 complex formed between the catalysts.[8c] These early examples have been revisited, and it appears that even with simple urea catalysts the role of urea is multifaceted.

More recent mechanistic models now include not only urea/proline catalyst interactions but also substrate/urea/proline interactions in the transition state. Companyó et al. speculated that the addition of a diarylthiourea enhances the acidity of proline's carboxylic acid and consequently stabilizes the transition state in the aldol reaction.[8c] Recently, our group observed that a urea tethered to a tertiary amine dramatically increased the rate of the α-aminoxylation and Mannich reactions.[8b] We hypothesized that the urea enhanced the rate-determining breakdown of the oxazolidinone intermediate, yielding the active enamine species. We demonstrated that the nature of the tether and the presence of the tertiary amine were critical parameters.

A similar conclusion was reached by Wang et al. in their study of a chiral bifunctional thiourea/L-proline-catalyzed Michael addition between an aldehyde and nitroolefins.[8f] Wang's system is complex as their reaction is also catalyzed by the thiourea alone with high enantioselectivity, albeit more slowly. Without the chiral thiourea additive, the proline-catalyzed reaction had 44% ee; addition of a chiral thiourea led to 90% ee. Switching the absolute configuration of the thiourea, however, had almost no effect on the absolute configuration of the resulting product, indicating that the stereochemistry of the reaction was controlled by L-proline.

While these examples begin to elucidate how ureas and proline interact to affect rate enhancements and alterations in product distribution, continued research into the urea/proline relationship is required to aid in the study and design of other urea/proline-catalyzed reactions. Here, we report a study of a thiourea/proline derivative-catalyzed synthesis of linear α-substituted tetrahydrofuran derivatives. Investigation of this reaction is particularly interesting as neither the proline derivative nor the thiourea can independently catalyze the reaction to any appreciable extent. Through investigation of this reaction, we offer new mechanistic insights into the role ureas play as cocatalysts.

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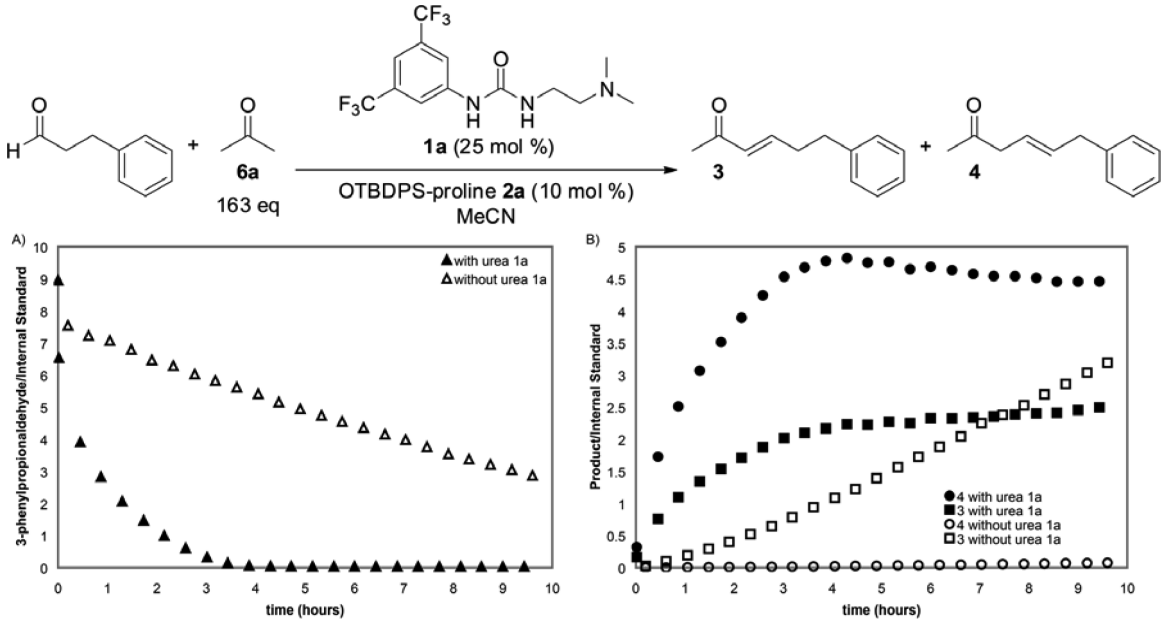
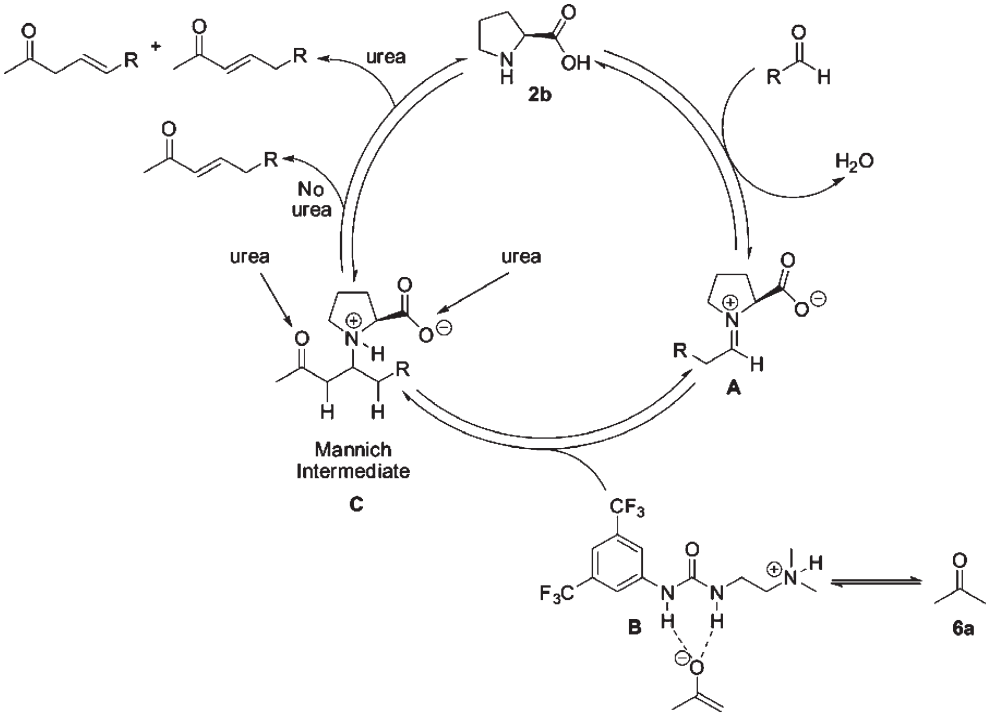


Figure 1. Reaction profiles for the aldol condensation reaction between 3-phenylpropionaldehyde and acetone. (A) Starting material consumption. (B) Appearance of products.

Scheme 1. Proposed Mechanism for Observed Elimination Products



RESULTS AND DISCUSSION

Prior Work: Aldol Reaction. From our work on the α-aminoxylation, we postulated that a variety of other proline-catalyzed reactions such as the aldol reaction could be accelerated using urea additives. Indeed, our hypothesis was supported by an initial study where we observed that *trans*-4-*tert*-butyldiphenylsilyloxy (OTBDPS) proline **2a** and urea **1a** accelerated the reaction between 3-phenylpropionaldehyde and acetone. Examination of the data shown in Figure 1(A) revealed that the reaction rate was accelerated in the presence of both **2a** and **1a**. We were surprised to observe that the product distribution for the proline derivative **2a** alone and the combination of **2a**/**1a** were different. The **2a** alone case produced **3** in vast majority, as has been previously noted by List and Wang, independently.[9] In contrast, the **2a**/**1a** system produced **4**, a previously unreported byproduct in the

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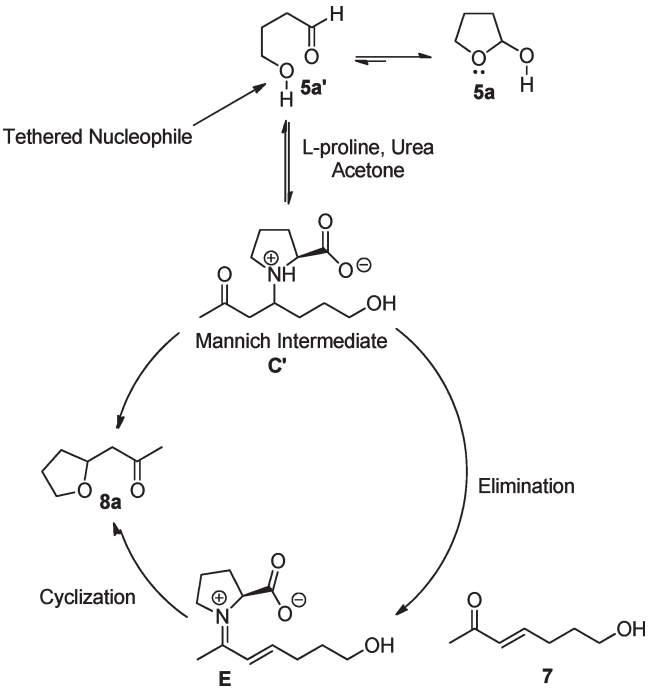
Scheme 2. Proposed Use of the Mannich Intermediate



aldol reaction, as the major product and **3** as the minor component (Figure 1(B)). Additionally, once the starting material was consumed, **4** was converted to **3**.

The observation that the combination of **2a**/**1a** yielded **4** prompted us to develop a new model (Scheme 1). We propose an extension of the "Mannich condensation"[10] mechanism described by List for the formation of enone byproducts in the aldol reaction.[9a] The catalytic cycle begins with the activation of the aldehyde by proline (or proline derivative) to give **A**, followed by the addition of acetone and subsequent elimination of proline from "Mannich Intermediate" **C** yielding the α,β-enone via the proline-only path. We propose that the addition of the urea accelerates the cycle by activating the enol form of acetone (**B**) that reacts with **A**. The observed alteration in product distribution in the presence of the urea is justified through the binding to intermediate **C**. Subsequent deprotonation by the pendant amine on the bifunctional urea finally gives rise to both the α,β- and β,γ-enones.

While the model provided a reasonable explanation for the altered product distribution in the presence and absence of the bifunctional urea, it did not provide insight into how to favor the formation of **3** or **4**. The model did, however, offer clues as to how we might use the Mannich Intermediate to produce cyclic ethers using substrates with tethered nucleophiles (Scheme 2). We envisioned two possible routes, each beginning with activation of the ring-opened form of 2-hydroxytetrahydrofuran **5a** with L-proline and acetone to give Mannich Intermediate **C′**. We hypothesized that cyclization would occur when the tethered nucleophile displaced proline via either direct S_N2 substitution of the Mannich Intermediate (**C′**) or Michael addition of **E** (Scheme 2).

Verification of Proposed Cyclization and Optimization of the Reaction. We tested the hypothesis articulated in Scheme 2 using the reaction between 2-hydroxytetrahydrofuran **5a** and methyl propyl ketone **6b**. Monitoring product formation as a function of time using the catalyst combination **2a**/**1a**, we observed that the reaction was rapid, finishing with ~80% yield (Figure 2).

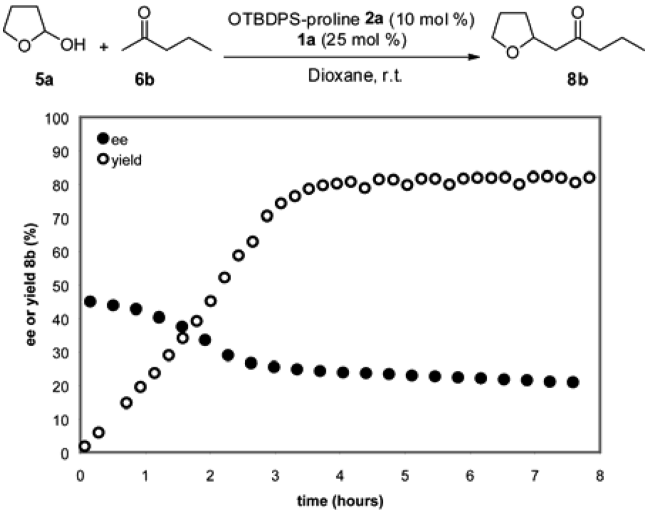
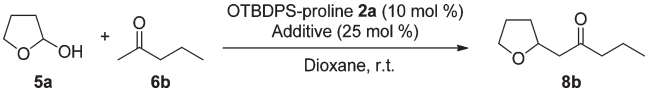
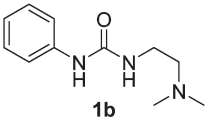
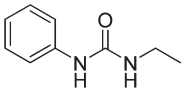
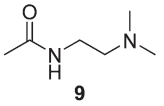


Figure 2. Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2a** in 1,4-dioxane. Reaction profile and enantioselectivity profile for 10 mol % OTBDPS-proline **2a**.

Table 1. Influence of Additives



Entry	Additive	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	None	<1	ND	26
2[c]	 **1b**	75	34	6
3	 **1c**	<5	ND	26
4	 **9**	31	51	28
5	 **10**	<5	ND	27
6	**1c** +**10**	69	5	29

[a] Determined by GC analysis using mesitylene as an internal standard. [b] Determined by GC analysis within 4 h of deeming the reaction complete. [c] Without OTBDPS-proline **2a**, reaction with **1b** has less than 1% yield in 27 h as determined by GC analysis. ND = Not determined.

The rate profiles observed were not asymptotic, suggesting complex kinetics. The plot of enantioselectivity as a function of time also underscores the complexity of the reactions, as it exhibits three distinct profiles. The enantioselectivity of the reaction was initially high and constant for the first hour, rapidly decreased during the second hour, and then slowly decreased after consumption of starting material (Figure 2).

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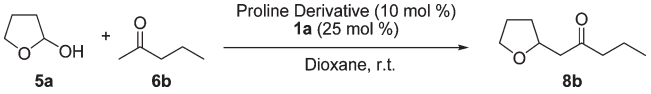
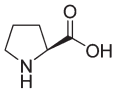
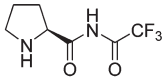
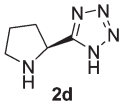
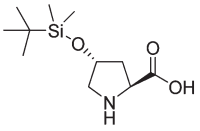
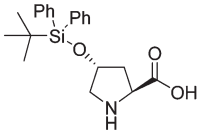
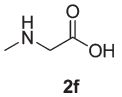
Table 2. Influence of Catalyst Structure



Entry	Catalyst	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	 **2b**	74	38	42
2	 TFA **2c**	NR	NA	42
3	 **2d**	<5	ND	42
4	 **2e**	77	19	3
5	 **2a**	74	27	4
6	 **2f**	NR	NA	24

[a] Determined by GC analysis using mesitylene as an internal standard. [b] Determined by GC analysis within 4 h of deeming the reaction complete. NR = No reaction; ND = Not determined.

In an effort to understand the change in enantioselectivity as a function of time and to potentially improve the enantioselectivity, we studied the influence of the urea and proline structure on the reaction. To begin, we examined the importance of the urea as an additive in the reaction and then the structural features of the urea that influenced the reaction yield and enantioselectivity.

From entry 1 (Table 1), we determined that **2a** alone could not catalyze the reaction. In addition, use of **1b** alone resulted in less than 1% yield after 27 h (data not shown). From these data, we concluded that both the urea and the proline derivative were necessary components in this reaction. We then performed a structure−activity relationship study to isolate which features of the urea were necessary. We found that both the urea functional group and a tethered amine were critical features (Table 1, entries 2−6). We observed that amide **9** catalyzed the reaction but with a lower overall yield at 28 h (Table 1, entry 4) and that **2a** (10 mol %), urea **1c** (25 mol %), and amine **10** (25 mol %) exhibited a slower rate and lower enantioselectivity (Table 1, entry 6), demonstrating the necessity of a bifunctional catalyst such as **1b**.

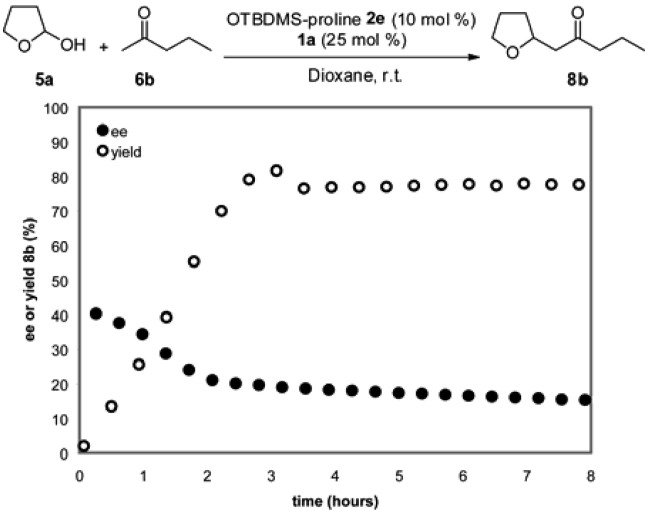


Figure 3. Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2e** in 1,4-dioxane. Reaction profile and enantioselectivity profile for 10 mol % OTBDMS-proline **2e**.

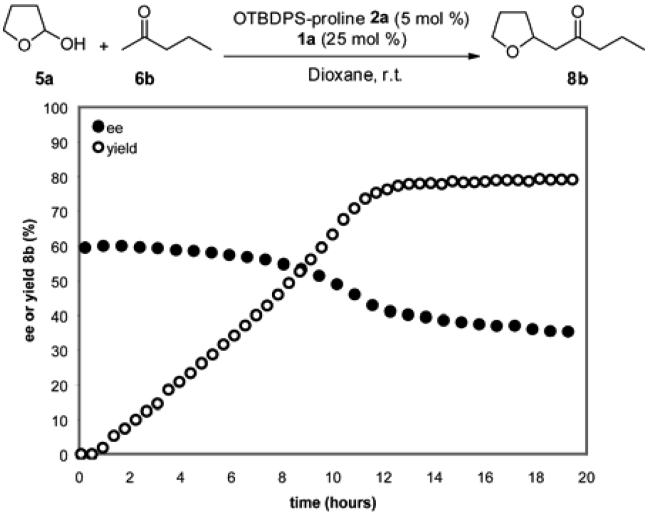
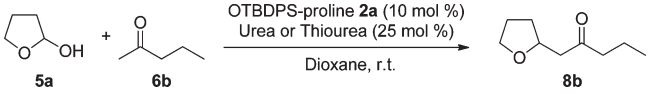
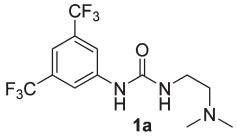
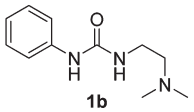
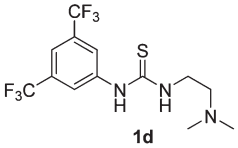
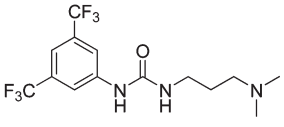
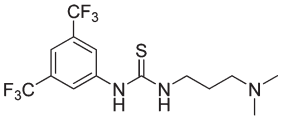
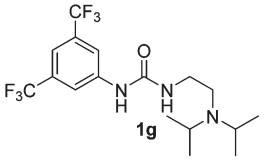
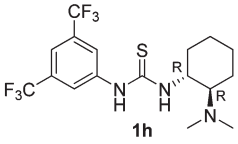
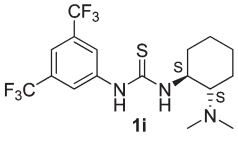


Figure 4. Reaction of 2-hydroxytetrahydrofuran and methyl propyl ketone in the presence of urea **1a** and proline derivative **2a** in 1,4-dioxane. Reaction profile and enantioselectivity profile for 5 mol % OTBDPS-proline **2a**.

We also studied the structural features of the proline derivative required for this transformation. The reaction did not proceed using proline derivative **2c** (developed by Wang for the construction of α,β-enones, Table 2, entry 2),[9b] tetrazole proline derivative **2d** (Table 2, entry 3), or *N*-methylglycine (Table 2, entry 6). We observed that only carboxylate-containing proline derivatives catalyzed the reaction and that 4-silyloxy-substituted proline derivatives provided the fastest reaction rates (Table 2, entries 1, 4, and 5). We found that the OTBDMS-proline derivative (**2e**) provided not only a faster rate but also a faster decrease in enantioselectivity relative to the OTBDPS-proline derivative (**2a**) (Figures 2 and 3).

Table 3. Influence of Urea Structure



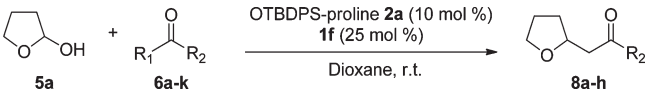
Entry	Additive	Yield (%)[a]	ee (%)[b]	Time (hrs)
1	 1a	74	27	4
2	 1b	75	34	6
3	 1d	74	36	4
4	 1e	74	27	5
5	 1f	74	35	5
6	 1g	71	6	9
7	 1h	73	34	22
8	 1i	74	34	9

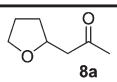
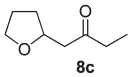
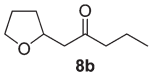
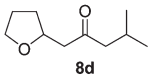
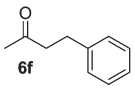
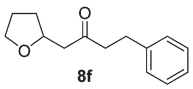
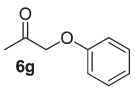
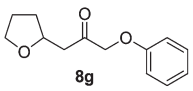
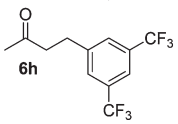
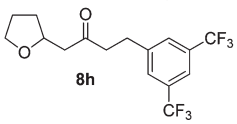
[a] Determined by GC analysis using mesitylene as an internal standard. [b] Determined by GC analysis within 4 h of deeming the reaction complete.

We then studied how the concentration of **2a** influenced the reaction's enantioselectivity. Interestingly, decreasing OTBDPS-proline **2a** loading to 5 mol % provided a 10% rise in the initial enantioselectivity of the reaction along with a 10% higher enantioselectivity at the conclusion of the reaction (Figure 4).

Finally, we concluded the catalyst structure study by examining the influence of different bifunctional ureas on the reaction. A suite of ureas and thioureas related to **1b**, including Takemoto's catalyst[11] (Table 3, entries 7 and 8), was examined. We found

Table 4. Scope of Substitution of 2-Hydroxytetrahydrofuran with Ketones



Entry	Ketone	Product	Yield (%)[b]	Time (hrs)
1[a]	 6a	 8a	40	4
2	 6c	 8c	78	6
3	 6b	 8b	81	5
4	 6d	 8d	69	8.5
5	 6e	NR	NR[c]	58
6	 6f	 8f	76	5
7	 6g	 8g	84	22
8	 6h	 8h	73	12

[a] Reaction run in CH_2Cl_2 due to high volatility of product. [b] Isolated yield. NR = No reaction. [c] 200 μmol reaction run with catalysts **2a** and **1a** in CH_2Cl_2, after 58 h GC analysis indicated the presence of mostly starting lactol. Enantioselectivities ranged from 0 to 48%; see Supporting Information.

that electron-withdrawing groups lead to enhanced reaction rate but decreased enantioselectivity (Table 3, entries 1 and 2), while using a thiourea resulted in only small gains in enantioselectivity (Table 3, entries 1, 3 and 4, 5). A longer linker between the urea and amine showed almost no change in rate or enantioselectivity (Table 3, entries 3, 5 and 1, 4), but increasing the steric bulk around the amine led to a slower reaction rate and decreased enantioselectivity (Table 3, entry 6). Optically active ureas did not improve the yield or enantioselectivity (Table 3, entries 7 and 8).

From these data, those presented above, and Table 6 in the Supporting Information, it is clear that both the proline derivative structure as well as structure and electronic properties of the urea are important factors influencing the yield, though no catalyst combination has yet to provide high enantioselectivity.

Using the optimized catalyst system **2a**/**1f**, we proceeded to evaluate the substrate scope with a variety of aliphatic ketones to determine which substrate structural biases exist and if the observed low enantioselectivities were a general feature of this method. We found that indeed enantioselectivities were low, ranging from 0 to 48% for the substrates studied (Table 4, entries

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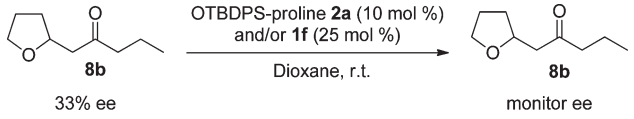
Table 5. Influence of Catalyst(s) on Enantiomeric Excess of 8b



entry	catalyst(s)	ee after 36 hrs (%)[a]
1	OTBDPS-proline **2a**	33
2	thiourea **1f**	33
3	OTBDPS-proline **2a** + thiourea **1f**	4

[a] Determined by GC analysis with an initial enantiomeric excess of 33% for the product. No evidence of product decomposition detected; see Supporting Information.

1−8, see Supporting Information). Aliphatic ketones were easily transformed to the corresponding cyclized products (Table 4, entries 1−4), though the ketone must be flanked by a methylene (Table 4, entry 2 versus entry 5). Ketones with flanking aryl ethers and benzylic groups also exhibited modest to high yields (Table 4, entries 6−8). From these data, we conclude that this dual catalyst method is an efficient strategy for construction of the C−C bond but that the system does not provide high enantioselectivity.

Origin of Decreasing Enantioselectivity. Prior to our work, the important mechanistic observation of decreasing enantioselectivity with time had not been reported in proline/urea cocatalyzed systems. We postulated initially that the decrease in enantiomeric excess was due to rapid product racemization. The configurational stability of **8b** was assessed by subjecting pure product with 33% enantiomeric excess to various catalyst combinations. Table 5 presents changes to the enantiomeric excess as a function of conditions over 36 h. We observed that the enantiomeric excess remains constant in the presence of thiourea **1f** or OTBDPS-proline derivative **2a** (Table 5, entries 1 and 2) alone but that the combination of the two caused a decrease from 33% to 4% enantiomeric excess in 36 h (Table 5, entry 3). These data indicate that slow erosion of ee once starting material was consumed can be explained by racemization of the product, but these data do not explain the rapid decrease in enantiomeric excess during the first phase of reaction (between 1 and 2 h). Addition of methyl propyl ketone did not alter this behavior.

We sought an experiment to help us explain the rapid decrease in enantioselectivity observed between the first and second hour of the reaction. Our original mechanistic model, as well as the model in the gold-catalyzed synthesis of substituted tetrahydropyrans from homopropargylic ethers, suggests an α,β enone as a potential intermediate for Michael-type cyclization strategies.[12] When enone **7** was subjected to our catalyst conditions, we found that both **1a** and **2a** alone catalyzed the ring closure of **7**. The rate of cyclization, however, was enhanced when both catalysts were used together (Figure 5). This observation indicates that **7** might be an intermediate along the reaction coordinate leading to the cyclization product. When we examined the configuration of **8a** when **7** was cyclized by **2a**/**1a**, we observed that the opposite enantiomer (−8% ee measured at 7.5 h) resulted compared to when lactol **5a** and acetone were cyclized in the presence of **2a** and **1f**.[13] As discussed below, we propose a mechanism whereby cyclization of intermediate **7** is competing with another

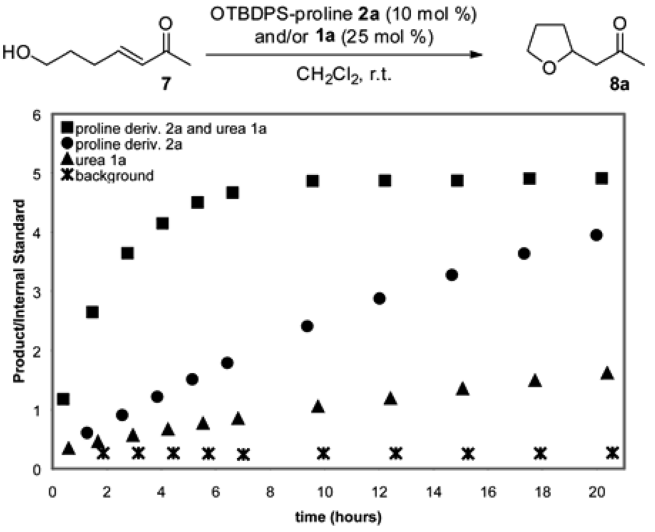


Figure 5. Subjection of enone **7** to catalyst conditions.

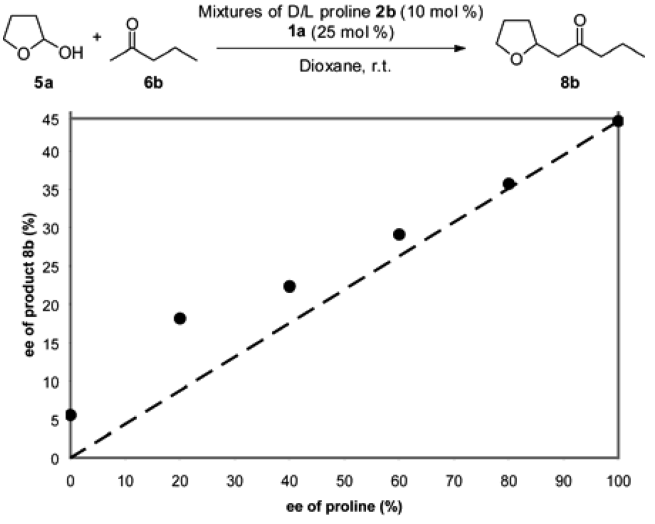


Figure 6. Relationship between enantioselectivity of the product **8b** and the enantiomeric excess of proline. Dashed line indicates expected enantiomeric excess of product. Samples were withdrawn, diluted into dichloromethane, and analyzed for enantioselectivity at 22 h before completion of the reaction.

cyclization mechanism and that the maximum rate of decreasing enantiomeric excess occurs when the two paths are operating simultaneously.

Before finalizing our mechanistic model, we determined if a nonlinear effect existed in our system. Nonlinear effects in proline-catalyzed reactions have been studied in a number of contexts.[8d,e,14] Though the reaction types differ, it is clear that the observation of nonlinear effects suggests that the active catalyst species is a complex of one or more species.[15]

We selected proline to study nonlinear effects because both enantiomers are commercially available. We examined the enantiomeric excess of our reaction as a function of L- and D-proline mole fraction. A small positive nonlinear effect was observed. When combined with our rate and decreasing enantiomeric excess with time data, these experiments suggest a complex composite mechanism for this reaction.

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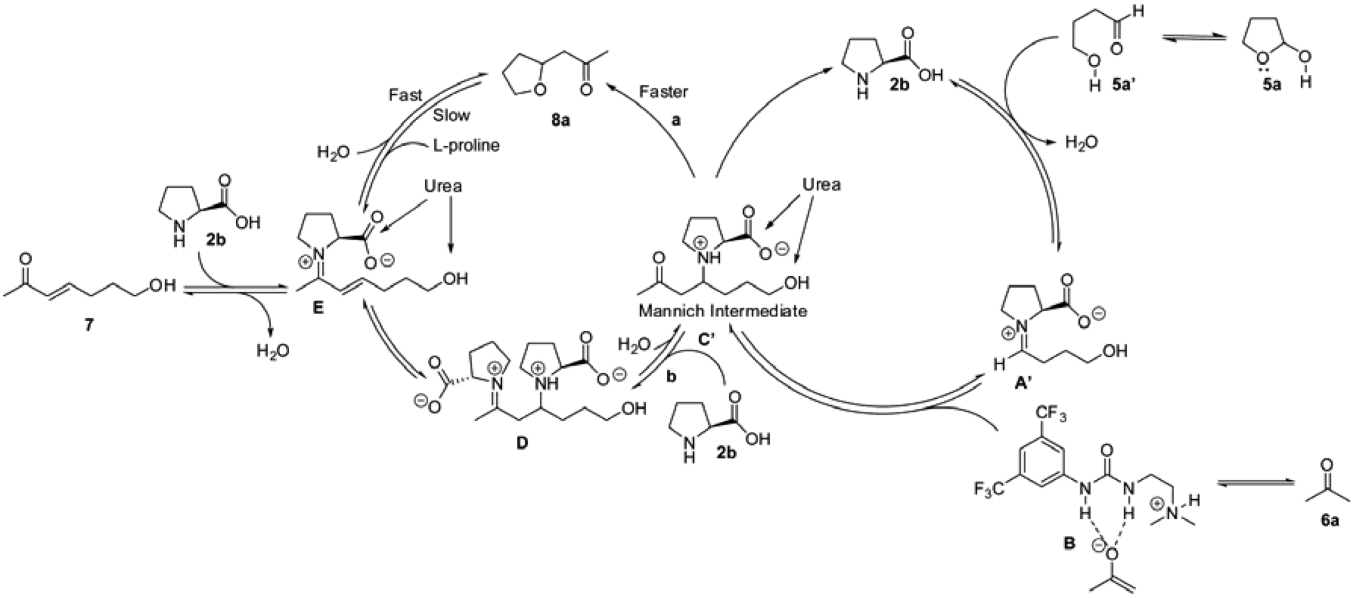
Scheme 3. Proposed Mechanism



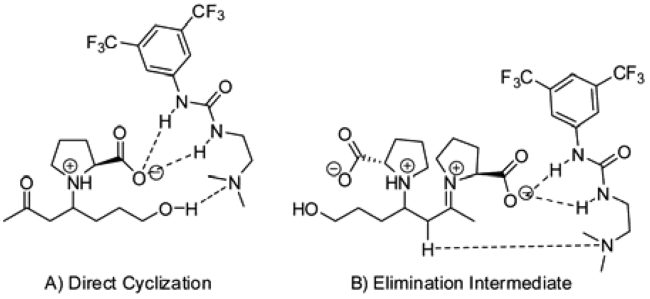


Figure 7. Possible interactions of urea with the Mannich Intermediate to provide (A) direct cyclization or (B) the α,β elimination intermediate.

Proposed Mechanism. With evidence for dramatic loss of enantioselectivity during the course of the reaction (Figure 2, 0−2 h), a much slower loss of enantiomeric excess after the reaction is complete (Figure 2, >2 h), and erosion of enantioselectivity when purified **8b** is subjected to reaction conditions (Table 5) and the nonlinear effect observed (Figure 6), we propose a model with two intertwined catalytic cycles with a common intermediate (Mannich Intermediate **C**′; Scheme 3) that can proceed down two pathways. Our model is an extension of mechanisms proposed by List, Cordova, Pihko, and Zeitler/Gschwind for aldol and Mannich condensation reactions.[9a,16] Starting from the upper right corner, **5a**′ reacts with L-proline to give iminium **A**′. A urea-activated ketone **B** then adds to **A**′ to give common Mannich Intermediate **C**′.

The rapid loss of enantioselectivity with time (Figures 2, 3, and 4) forced us to consider multiple pathways for **C**′, with one path dominating in the first phase of the reaction and an alternative path whose rate increases as a function of changing reaction conditions. In the dominant early path, we propose the urea binds to the carboxylate anion in **C**′ as is speculated for many urea-catalyzed processes.[17] The tethered amine then deprotonates the alcohol leading to direct cyclization exhibiting high enantioselectivity (Scheme 3, route a, Figure 7(A)). At high aldehyde/lactol **5a** concentrations (first hour), we propose that the proline is largely bound to the starting material. Once the lactol concentration decreases, the increase in free proline opens the diproline pathway (intermediate **D**) that proceeds through enone **E**. This causes a subsequent drop in the enantiomeric excess because the enone pathway provides the opposite enantiomer, as we observed when **7** was subjected to reaction conditions.

This model is supported by our observation that a decrease in the initial proline derivative concentration from 10 mol % to 5 mol % resulted in a 10% greater initial enantioselectivity. These data suggest that the second order in the proline path is suppressed when the total proline-derivative concentration is low. In addition, the observed nonlinear effects observed suggest that a diproline-derivative path is possible. Finally, others have reported that diproline intermediates are present in aldol condensation reactions[16a,b] (as well as other proline-catalyzed reactions).[18]

Most recently, Zeitler and Gschwind used NMR to investigate the mechanism of the proline-catalyzed aldehyde self-condensation. The researchers observed differences in the rate of formation for the aldol product versus aldol condensation product (elimination products similar to those observed in Figure 1, compounds **3** and **4**) when varied catalyst loadings were used. From these experiments, the authors support the earlier mechanistic work that the aldol condensation utilizes two proline molecules in the rate-determining step.[16c]

In our case, we hypothesize that the urea binds to the less hindered proline in intermediate **D**. Deprotonation of the α hydrogen results in α,β elimination product **E** with a single proline still bound (Scheme 3 route b, and Figure 7(B)). **E** then cyclizes to give product **8a**. Thus, the observed rapid loss of enantioselectivity between hours 1 and 2 is the result of the elimination pathway operating at a different rate than the direct cyclization pathway. The slow erosion of enantiomeric excess after the lactol is consumed is due to product racemization

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(Scheme 3). Likewise, Zeitler/Gschwind attributed the erosion of diastereoselectivity during the proline-catalyzed aldehyde self-condensation to the changing rates of aldol addition, aldol condensation, and retro-aldolization reactions.[16c] In addition, Massi et al. observed epimerization of α-C-glycosylmethyl ketones in the presence of proline. These authors propose an intermediate similar to **E** shown in Scheme 3.[19]

CONCLUSION

We developed a dual organocatalyst system using a bifunctional thiourea and proline derivative to efficiently catalyze the formation of α-substituted tetrahydrofuran/pyran derivatives. Decreasing enantioselectivity and complex reaction kinetics led us to propose that the thiourea/proline system operates via two competing reaction routes. We proposed one route that dominates at the beginning of the reaction and involves direct cyclization of a Mannich-like intermediate, providing moderate enantioselectivity. As the reaction proceeds, free proline becomes available, and a second diproline intermediate based pathway that produces the opposite enantiomer begins to dominate. Upon completion of the reaction, product racemization occurs resulting in continued erosion of enantiomeric excess by the dual catalyst system. Currently, this method operates with moderately high yields; we believe it can be made highly enantioselective once catalysts that can divert the pathway to one dominant mechanism are designed.

EXPERIMENTAL SECTION

General Information. Catalyst screening reactions were performed in 2 mL vials and reactions monitored by gas chromatography by direct sampling of the stirred reaction vials. Glass, gastight syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel (230−400 mesh). For analytical thin layer chromatography (TLC), silica gel 60 F_{254} plates were used. All commercial reagents were used without further purification with the following exceptions: dichloromethane for air-sensitive reaction was dried by passing through columns packed according to the procedure of Timmers.[20] Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration.

Instrumentation. Gas chromatographic (GC) analyses for substituted tetrahydrofuran synthesis experiments were performed using a GC equipped with an autosampler, a flame ionization detector (FID), and a column with dimensions 30 m × 0.319 mm × 0.25 μm. The temperature program for GC analysis held the temperature constant at 80 °C for 1 min, heated samples from 80 to 250 °C at 25 °C/min, and held at 250 °C for 2 min. Inlet and detector temperatures were set constant at 250 and 300 °C, respectively. For α,β β,γ work the analysis held the temperature constant at 80 °C for 1 min, heated the samples from 80 to 200 °C at 17 °C/min, and held at 200 °C for 1.94 min. Inlet and detector temperatures were set constant at 220 and 250 °C, respectively. Mesitylene was used as an internal standard to calculate reaction conversion and calibrate yields.

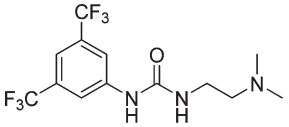
We previously reported the synthesis of **1b**.[8b]

Wei Wang catalyst **2c** was prepared following literature procedure, and the ^{1}H NMR spectrum matched the previously reported spectrum.[9b]

Lactol **5a** was prepared following literature procedure, and the ^{1}H NMR matched the previously reported spectrum.[21]

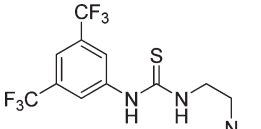
EXPERIMENTAL METHODS

Amine/Urea/Thiourea Preparation.



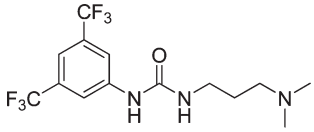
1a

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)urea ***1a***. To a solution of 3,5-bis(trifluoromethyl) phenyl isocyanate (0.50 mL, 2.90 mmol, 1 equiv) in ethyl acetate (30 mL) was added *N*, *N*′-dimethylethylenediamine (0.35 mL, 3.19 mmol, 1.1 equiv). The reaction was stirred at room temperature for 24 h and then concentrated in vacuo. The crude product was then recrystallized from 10% ethyl aceate/90% hexanes and washed with cold hexanes to yield **1a** (0.55 g, 55%) as white crystals. Mp 137−139 °C. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.02 (s, 2H), 7.50 (s, 1H), 3.37 (t, J = 6.54 Hz, 2H), 2.52 (t, J = 6.51 Hz, 2H), 2.32 (s, 6H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 157.4, 143.5, 133.2 (q, J = 32.99 Hz), 124.9 (q, J = 271.75 Hz), 119.0, 115.4 (m), 59.8, 45.5, 38.5 ppm. Anal. calcd for $C_{13}H_{15}F_6N_3O$: C, 45.49; H, 4.40; N, 12.24. Found: C, 45.49; H, 4.30; N, 12.20.



1d

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl) thiourea ***1d***.[22] To a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.5 mL, 2.74 mmol, 1.0 equiv) in ethyl acetate (30 mL) was added *N*,*N*-dimethylethylenediamine (0.33 mL, 3.01 mmol, 1.1 equiv). The reaction was stirred at room temperature for 24 h and then concentrated in vacuo. The crude product was then recrystallized from 10% ethyl acetate/hexanes and washed with cold hexanes to yield **1d** (0.892 g, 91%) as white fluffy crystals. Mp 143−145 °C. ^{1}H NMR: (600 MHz, CD_3OD) δ8.21 (s, 2H), 7.62 (s, 1H), 3.76 (bs, 2H), 2.62 (t, J = 6.48 Hz, 2H), 2.33 (s, 6H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 182.9, 143.2, 132.8 (q, J = 33.30 Hz), 124.8 (q, J = 271.83 Hz), 123.7, 117.8, 58.6, 45.5, 43.0 ppm. Anal. calcd for $C_{13}H_{15}F_6N_3S$: C, 43.45; H, 4.21; N, 11.69. Found: C, 43.48; H, 4.09; N, 11.68.



1e

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)propyl) urea ***1e***. To a solution of 3,5-bis(trifluomethyl) phenyl isocyanate (0.50 mL, 2.89 mmol, 1 equiv) in ethyl acetate (30 mL) was added 3-(dimethylamino)-1-propylamine (0.40 mL, 3.18 mmol, 1.1 equiv). The reaction was stirred at room temperature for 24 h and then concentrated in vacuo. The crude product was then recrystallized from 10% ethyl aceate/90% hexanes and washed with cold hexanes to yield **1e** (0.965 g, 93%) as slightly yellow crystals. Mp 92−95 °C. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.02 (s), 7.46 (s), 3.27 (t, J = 6.84 Hz,

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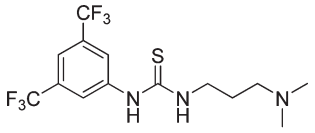
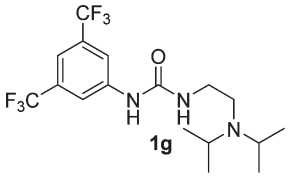
2H), 2.40 (t, J = 7.62 Hz, 2H), 2.26 (s, 6H), 1.75 (m, J = 7.23 Hz, 2H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ157.4, 143.5, 133.1 (q, J = 33.02 Hz), 124.9 (q, J = 271.80 Hz), 119.0, 115.4 (t, J = 3.69 Hz), 58.1, 45.5, 39.2, 28.7 ppm. Anal. calcd for $C_{14}H_{17}F_6N_3O$: C, 47.06; H, 4.80; N, 11.76. Found: C, 47.32; H, 4.77; N, 11.78.



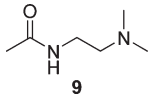
1f

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)propyl) urea ***1f***.[22] To a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.5 mL, 2.74 mmol, 1 equiv) in ethyl acetate (27 mL) was added 3-(dimethylamino)-1-propylamine (0.380 mL, 3.01 mmol, 1.1 equiv). The reaction was stirred at room temperature for 24 h and then concentrated in vacuo. Initially the product was chromatographed with 10% MeOH/CH_2Cl_2 to give an oil that solidified upon standing. Later, it was found that the crude product could also be recrystallized from diethyl ether/pentane and washed with cold pentane. A seed crystal could be added to aid in crystallization to yield **1f** (670.9 mg, 66%) as white crystals. Mp 83−86 °C. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.19 (s, 2H), 7.66 (s, 1H), 3.66 (bs, 2H), 2.44 (t, J = 7.44 Hz, 2H), 2.27 (s, 6H), 1.86 (m, J = 7.20 Hz, 2H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 182.9, 143.2, 132.8 (q, J = 33.35 Hz), 124.8 (q, J = 271.79 Hz), 124.0 (m), 118.0, 58.3, 45.4, 44.0, 27.5 ppm. Anal. calcd for $C_{14}H_{17}F_6N_3S$: C, 45.04; H, 4.59, N, 11.25. Found: C, 45.11; H, 4.54; N, 11.32.



1g

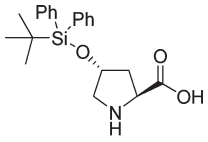
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(diisopropylamino)ethyl) urea ***1g***. To a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (0.5 mL, 2.90 mmol, 1 equiv) in ethyl acetate (30 mL) was added *N*,*N*-diisopropylethylenediamine (0.56 mL, 3.19 mmol, 1.1 equiv). The reaction was stirred at room temperature for 24 h and then concentrated in vacuo. The crude product was then recrystallized from 3% ethyl acetate/hexane and washed with cold hexanes to yield **1g** (0.9146 g, 79% yield) as white crystals. Mp 152−154 °C. ^{1}H NMR: (600 MHz, CD_3OD) δ 8.03 (s, 2H), 7.50 (s, 1H), 3.24 (t, J = 6.81 Hz, 2H), 3.09 (m, J = 6.56 Hz, 2H), 2.65 (t, J = 6.81 Hz, 2H), 1.09 (d, J = 6.54 Hz, 12H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 157.5, 143.6, 133.2 (t, J = 49.52 Hz), 124.9 (q, J = 271.65 Hz), 118.9, 115.4, 50.0, 45.7, 41.2, 20.9 ppm. Anal. calcd for $C_{17}H_{23}F_6N_3O$: C, 51.13; H, 5.80; N,10.52. Found: C, 51.34; H, 5.78; N, 10.52.



9

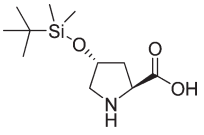
N-(2-(Dimethylamino)ethyl)acetamide ***9***. Following literature method with minor modifications.[23] To a solution of triethylamine (1.4 mL, 0.11 mmol, 1.1 equiv) in dichloromethane (20 mL) cooled to 0 °C was added *N*,*N*-dimethylethylenediamine (1 mL, 9.19 mmol, 1.0 equiv). Then acetyl chloride (0.682 mL, 9.59 mmol, 1.0 equiv) was added dropwise over the course of 15 min by syringe pump. The reaction was allowed to warm to room temperature and stirred for ~3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The product was chromatographed (silica gel, 10% MeOH/CH_2Cl_2) to afford **9** as a light yellow oil (120.8 mg, 10%). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.08 (brs, 1H), 3.33 (q, J = 5.6 Hz, 2H), 2.42 (t, J = 5.9 Hz, 2H), 2.24 (s, 6H), 1.99 (s, 3H) ppm.^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 57.8, 45.1, 36.8, 23.3 The proton and carbon spectral data were in accordance with those described in the literature.[23]

Proline Derivative Preparation. *General Procedure:*[24]. *trans*-4-Hydroxy-L-proline (787 mg, 6 mmol, 1 equiv) was placed in a round-bottom, and acetonitrile (10 mL) was added. The appropriate silane (21 mmol, 3.5 equiv) was added. The reaction was cooled to 0 °C, and DBU (22.2 mmol, 3.7 equiv) was added. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction was then quenched with pentane and the actonitrile layer washed with pentane 3 times. The pentane extracts were combined and concentrated. Methanol (32 mL), THF (16 mL), water (16 mL), and 2 N NaOH (24 mL) were added to the resulting oil and allowed to stir at room temperature for 90 min. The solution was then titrated to a pH of 6 with 1 M HCl. The solvents were then removed under reduced pressure, and the appropriate workup and crystallization procedure (shown below) was used.



2a

(2S,4R)-4-(tert-Butyldiphenylsilyloxy)pyrrolidine-2-carboxylic Acid ***2a***.[25] Following general procedure. The organic solvents were removed under reduced pressure. To the resulting clear water layer, diethyl ether was added in a ~1:1 diethyl ether/water ratio. Crystals should then form on the interface of the water diethyl ether layer. Crystals are then filtered and washed with cold diethyl ether to afford white crystals (1.65 g, 75% yield). ^{1}H NMR: (600 MHz, CD_3OD) δ 7.68−7.59 (m, 4H), 7.49−7.36 (m, 6H), 4.57 (bs, 1H), 4.25 (dd, J = 7.56, 10.32 Hz, 1H), 3.30 (dd, J = 4.04, 12.32 Hz, 1H), 3.19 (d, J = 12.30 Hz, 1H), 2.33 (tdd, J = 1.84, 7.54, 13.59 Hz, 1H), 1.92 (ddd, J = 3.93, 10.20, 13.80 Hz, 1H), 1.07 (s, 9H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ 173.7, 136.97, 136.95, 134.2, 134.1, 131.5, 129.2, 74.2, 61.8, 54.7, 39.9, 27.5, 20.0 ppm. The proton spectrum closely resembles that in the literature, but updated splittings are provided.[25]



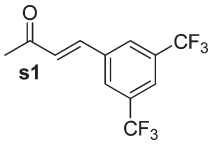
2e

(2S,4R)-4-(tert-Butyldimethylsilyloxy)pyrrolidine-2-carboxylic Acid ***2e***.[25] Following general procedure using 2.358 g of *trans*-4-hydroxy-L-proline. The solvents are removed under reduced pressure with heating to 40 °C until a white precipitate just begins to form. At this point, water was added until all the precipitate goes into solution. The solution was then allowed to sit until crystals form. The crystals were filtered and washed with diethyl ether to afford white crystals (3.08 g, 70% yield). ^{1}H NMR: (600 MHz, CD_3OD) δ 4.66 (m, 1H), 4.19 (dd, J = 7.59, 10.41 Hz, 1H), 3.44 (dd, J = 3.78, 12.12 Hz, 1H), 3.18 (td, J = 1.65, 12.12 Hz, 1H), 2.34 (tdd, J = 1.91, 7.55, 13.52 Hz, 1H), 2.09 (ddd, J = 3.78, 10.20, 13.74 Hz, 1H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm. ^{13}C NMR: (151 MHz, CD_3OD) δ 174.0, 73.3, 61.7, 55.1, 40.2, 26.3, 19.0, −4.7, −4.8 ppm. The proton is in accordance with that described in the literature.[25]

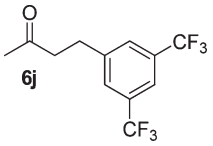
Starting Material Synthesis.

(3,5-Bis(trifluoromethyl)phenyl)but-3-en-2-one ***s1***.[26] A solution of 3,5-bis(trifluoromethyl)benzaldehyde (4 mL, 22.06 mmol, 1.1 equiv) and 1-(triphenylphosphoranylidene)-2-propanone (7.02 g, 22.06 mmol, 1.0 equiv) in chloroform (110 mL) was heated to reflux for 4 h. The mixture was cooled to room temperature; silica gel was added; and the

solvent was concentrated in vacuo. The resulting powder was purified by column chromatography on silica gel with 5% ethyl aceate/hexanes to



afford **s1** (6.18 g, 99% yield). Mp 48.5−50 °C. ^{1}H NMR: (600 MHz, $CDCl_3$) 7.97 (s, 2H), 7.89 (s, 1H), 7.55 (d, J = 16.26 Hz, 1H), 6.84 (d, J = 16.32 Hz, 1H), 2.43 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) 197.1, 139.3, 136.7, 132.6 (q, J = 33.67 Hz), 130.0, 127.8, 123.5 (m), 123.0 (q, J = 272.96 Hz), 28.1 ppm. HRMS (EI+): calcd for $C_{12}H_8F_6O$, 282.0479; found 282.0480.

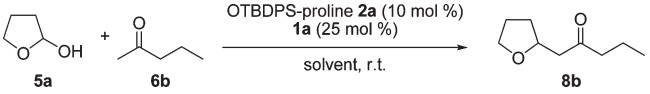


4-(3,5-Bis(trifluoromethyl)phenyl)butan-2-one ***6j***. Prepared following a previously reported method:[27] A solution of bis(cyclopentadienyl)titanium dichloride (0.262 g, 1.095 mmol, 0.05 equiv), triethylamine hydrochloride (15.07 g, 110 mmol, 5 equiv), and zinc dust (3.58 g, 54.8 mmol, 2.5 equiv) in dichloromethane (164 mL) was prepared and stirred until the solution turned from red to green. A solution of **s1** (6.18 g, 21.90 mmol) in dichloromethane (274 mL) was added. The reaction was stirred for 24 h. The reaction was quenched with NH_4Cl and then passed through Celite and extracted with ether. The combined organic fractions were washed with brine and dried with $MgSO_4$ and concentrated. The residue was purified by krughror distillation at 50 °C under vacuum. Then the product was dissolved in CH_2Cl_2 and stirred with charcoal, passed through Celite, evaporated, and dried under vacuum to give **6j** as a slightly yellow colored oil (4.1 g, 66% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.68 (s, 2H), 3.04 (t, J = 7.38 Hz, 2H), 2.87 (t, J = 7.38, 2H), 2.18 (s, 3H) ppm. ^{13}C NMR: (151 MHz, $CDCl_3$) 206.2, 143.7, 131.6 (q, J = 33.08 Hz), 128.6, 123.3 (q, J = 272.49 Hz), 120.1 (m, J = 3.80 Hz), 44.0, 29.7, 29.0 ppm. HRMS (EI+): calcd for $C_{12}H_{10}F_6O$, 284.0636; found 284.0631. Proton and carbon spectra were in accordance with those previously published for **6j**.[28]

SCREENING CONDITIONS

Solvent Screen. The proline derivative **2a** (11.1 mg) was weighed into 2 mL vials. A 0.15 M stock solution of urea catalyst **1a** (25.7 mg, 75 μmol, 0.25 equiv) was prepared in chloroform, and 500 μL was dispensed into the vials. Solvent was evaporated overnight at 30 °C followed by drying under vacuum. A stock solution of starting materials 2-hydroxytetrahydrofuran (0.306 M), and methyl propyl ketone (1.53 M) was prepared in each solvent using a density of 1.084 g/mL for 2-hydroxytetrahydrofuran. A stock solution of mesitylene (0.100 M) was also prepared in each solvent. An amount of 220 μL of each respective solvent was added to the vials, followed by 300 μL of the mesitylene stock. The reactions were initiated with 980 μL of the starting material stock. The reactions were stirred at room temperature and monitored by GC, and yields were calculated from a calibration curve of product with reference to the mesitylene internal standard. After 24 h, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL dichloromethane and the enantioselectivity analyzed by chiral GC.

Table 6. Solvent Screen



entry	solvent	yield (%)[a]	ee (%)[b]	time (hrs)
1	MeOH	82	−5	15
2	DMF	74	−2	13
3	MeCN	84	4	12
4	1,4-dioxane	82	11	8
5	$CHCl_3$	41	57	25
6	CH_2Cl_2	66	47	24

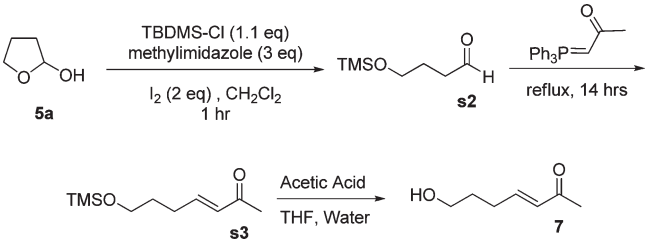
[a] Determined by GC analysis using mesitylene as an internal standard. [b] Determined by chrial GC analysis of crude reaction mixture at 24 h.

Proline Derivative Screen. Each proline derivative (30.0 μmol, 0.10 equiv) and urea catalyst **1a** (25.7 mg, 75 μmol, 0.25 equiv) was weighed into 2 mL vials. The reactions were initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20 M, 1 equiv), methyl propyl ketone (1500 μmol, 1500 μL, 1 M, 5 equiv), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 equiv). The reactions were stirred at room temperature and monitored by GC, and yields were calculated from a calibration curve of pure product in reference to the mesitylene internal standard. Upon deeming the reaction complete, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL of dichloromethane and the enantioselectivity analyzed by chiral GC.

Amine/Urea/Thiourea Additive Screen. Proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 equiv) and urea/amine/additive catalysts (75 μmol, 0.25 equiv) were weighed directly into 2 mL vials. The reactions were initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20 M, 1 equiv), methyl propyl ketone (1500 μmol, 1500 μL, 1 M, 5 equiv), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 equiv). The reactions were stirred at room temperature and monitored by GC, and yields were calculated from a calibration curve of pure product in reference to the mesitylene internal standard. Upon the reaction being deemed complete, an aliquot (amount depended on the yield of the reaction) was removed and diluted into ~200 μL of dichloromethane and the enantioselectivity analyzed by chiral GC.

MECHANISM AND SELECTIVITY EXPERIMENTS

Synthesis of the Suggested Enone Intermediate



Synthesis of 4-(tert-Butyl-dimethylsilyloxy)butyraldehyde ***s2***. Following a previously reported method:[29] A stirred solution of

5a (1.0 g, 11.35 mmol, 1 equiv), methylimidazole (2.7 mL, 34.1 mmol, 3 equiv), and iodine (5.76 g, 22.70 mmol, 2 equiv) in dichloromethane (30 mL) was prepared. *tert*-Butyldimethylsilyl chloride (1.882 g, 12.49 mmol, 1.1 equiv) was then added and the reaction allowed to stir for 1 h. The solvent was then concentrated. The residue was dissolved in ethyl acetate and washed with saturated aq $Na_2S_2O_3$ until the color went from orange to clear, indicating all the iodine was quenched. The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by column chromatography 2% ethyl acetate/hexane to provide (0.9264 g, 40%) ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.75 (t, J = 1.71 Hz, 1H), 3.61 (t, J = 5.97 Hz, 2H), 2.46 (dt, J = 1.74, 3.54 Hz, 2H), 1.82 (m, 2H), 0.84 (s, 9H), 0 (s, 6H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 202.5, 62.1, 40.8, 25.9, 25.5, 18.3, −5.4 ppm. Proton and carbon spectra match previously published spectra.[30]

Synthesis of 7-(tert-Butyl-dimethylsilyloxy)butyraldehyde ***s3***. A solution of **s2** (0.9264 g, 4.58 mmol, 1.1 equiv) and 1-(triphenylphosphoranylidene)-2-propanone (1.32 g, 4.16 mmol, 1 equiv) in 20 mL of $CHCl_3$ was prepared. The reaction was allowed to stir at reflux for 15 h. The reaction was cooled, and silica gel was added to the reaction mixture. The solvent was then concentrated and the powder directly chromatographed with 5% EtOAc/Hexanes to yield (570.6 mg, 57% yield). ^{1}H NMR: (600, $DDCl_3$) δ 6.78 (td, J = 6.87, 15.96 Hz, 1H), 6.04 (td, J = 1.50, 15.96 Hz, 1H), 3.59 (t, J = 6.15 Hz, 2H), 2.25 (dq, J = 1.40, 2.25 Hz, 2H), 2.19 (s, 3H), 1.64 (m, J = 6.87 Hz, 2H), 0.85 (s, 9H), 0 (s, 6H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 198.5, 148.1, 131.4, 62.2, 31.2, 29.0, 26.8, 25.9, 18.3, −5.4 ppm. Proton spectrum matched previously published spectrum.[26]

Synthesis of 7-Hydroxy-3-heptene-2-one ***7***. Following previously reported method:[31] A solution of acetic acid (7.7 mL), water (3.9 mL), and THF (3.9 mL) was prepared and added to **s3** (554.2 mg, 2.103 mmol). The reaction was allowed to stir at room temperature for 2 h. Longer stirring times resulted in the formation of cyclized product **8a**. At the end of 2 h, diethyl ether was added, and a saturated aqueous solution of Na_2CO_3 was added to neutralize the reaction. The organic layer was then washed 2 times with the saturated aqueous solution of Na_2CO_3 followed by 1 time with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated. The product was purified by column chromatography using 70% EtOAc/hexane to give alcohol **7** as an oil (18.3 mg, 7% yield). ^{1}H NMR: (600, $DDCl_3$) δ 6.84 (td, J = 6.87, 15.96 Hz, 1H), 6.11 (td, J = 1.50, 15.96 Hz, 1H), 3.69 (t, J = 6.41 Hz, 2H), 2.35 (m, 2H), 2.25 (s, 3H), 1.75 (m, 2H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 198.7, 147.7, 131.5, 61.9, 31.0, 28.8, 26.9, 26.9 ppm. The coupling constants are consistent with those expected for a *trans* product. The proton spectrum matched the corresponding peaks in the previously reported spectrum.[31]

Exposure of Suggested Enone Intermediate to Reaction Conditions. Proline derivative **2a** (1.8 mg, 4.80 μmol, 0.10 equiv) and/or urea **1a** (4.12 mg, 12.0 μmol, 0.25 equiv) were weighed directly into 2 mL GC vials containing 250 μL inserts. The reactions were initiated with 240 μL of a stock solution containing: enone **7** (240 μL, 48 μmol of 0.2 M solution in CH_2Cl_2) and mesitylene (240 μL, 4.80 μmol of 0.02 M solution in CH_2Cl_2). The reactions were stirred at room temperature and monitored by GC.

Plot of Reaction Progress and Decay of Enantioselectivity During Reaction. *Proline Derivative* ***2e****: 10 mol %.* Proline derivative **2e** (7.4 mg, 30.0 μmol, 0.05 equiv) and urea **1a** (25.7 mg, 75 μmol, 0.25 equiv) were weighed directly into 2 mL vials. The reaction was initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20 M, 1 equiv), methyl propyl ketone (1500 μmol, 1500 μL, 1 M, 5 equiv), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 equiv). The reactions were stirred at room temperature, monitored by GC for yield and enantioselectivity directly. The split ratio and sample size were changed during the course of the reaction to get an adequate response.

Proline Derivative ***2a****: 10 mol %.* Proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 equiv) and urea **1a** (25.7 mg, 75 μmol, 0.25 equiv) were weighed directly into 2 mL vials. The reaction was initiated with 1500 μL of a stock solution containing: 2-hydroxytetrahydrofuran (300 μmol, 1500 μL, 0.20 M, 1 equiv), methyl propyl ketone (1500 μmol, 1500 μL, 1 M, 5 equiv), and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 equiv). The reactions were stirred at room temperature and monitored by GC for yield and enantioselectivity directly. The split ratio and sample size were changed during the course of the reaction to get an adequate response.

Proline Derivative ***2a****: 5 mol %.* Proline derivative **2a** (67 mg, 0.180 mmol, 0.05 equiv) and urea **1a** (309 mg, 0.900 mmol, 0.25 equiv) were weighed directly into a 20 mL vial. The reaction was initiated with 18 mL of a stock solution containing: 2-hydroxytetrahydrofuran (3.60 mmol, 18 mL, 0.20 M, 1 equiv), methyl propyl ketone (18 mmol, 18 mL, 1 M, 5 equiv), and mesitylene (0.360 mmol, 18 mL, 0.02 M, 0.10 equiv) in 1,4-dioxane. During the course of the reaction, aliquots of the reaction mixture (amounts varied to ensure adequate sample for analysis) were removed and either directly analyzed or diluted into dichloromethane and enantioselectivities determined by chiral GC analysis. At ∼7 h an aliquot was removed, continuously stirred and directly analyzed for enantioselectivity by GC (adjusting the split ratio and sample size) for the remainder of the time.

Decay of Product Enantioselectivity Under Various Reaction Conditions. A series of reactions were set up containing various combinations of catalysts and reactants. The respective 2 mL vials were prepared with the following amounts of catalyst/starting materials: thiourea **1f** (28.0 mg, 75 μmol, 0.25 equiv), proline derivative **2a** (11.1 mg, 30.0 μmol, 0.10 equiv), and methyl propyl ketone (128 μL, 1200 μmol, 4 equiv). The reactions were initiated with 1500 μL of a stock solution containing: product **8b** (300 μmol, 1500 μL, 0.20 M, 1 equiv) and mesitylene (30.0 μmol, 1500 μL, 0.02 M, 0.10 equiv) in 1,4-dioxane. After 36 h the enantioselectivity of the reaction was assessed by withdrawing ∼32 μL aliquots of the reaction mixture and diluting into ∼200 μL dichloromethane to give ∼0.032 M product concentration. Enantioselectivities were then determined by chiral GC analysis.

Nonlinear Effect Experiments. A series of reactions were set up containing various mole fractions of D- and L-proline (see Table 7). Urea **1a** (171.6 mg, 0.5 mmol, 0.25 equiv) was added to the vials. The reactions were initiated with 10 mL of a stock solution containing: 2-hydroxytetrahydrofuran (2 mmol, 10 mL, 0.20 M, 1 equiv), methyl propyl ketone (10 mmol, 10 mL, 1 M, 5 equiv), and mesitylene (0.2 mmol, 10 mL, 0.02 M, 0.10 equiv) in 1,4-dioxane. The reactions were vigorously stirred for 22 h upon which an aliquot was removed, diluted into dichloromethane, and analyzed for yield and enantiomeric excess by GC analysis (Figure 8).

CHARACTERIZATION OF PRODUCTS

General Procedure. 2-Hydroxytetrahydrofuran (1.14 mmol, 100 mg, 1 equiv) was added to a 20 mL vial and equipped with a stir bar. Dioxane (5.7 mL, 200 mM) was added. The appropriate

Table 7. Amounts of D-and L-Proline Used

entry	ee of proline (%)	D-proline (mg)	L-proline (mg)
1	100	0	23.1
2	80	2.3	20.6
3	60	4.6	18.4
4	40	6.9	16.2
5	20	9.2	13.8
6	0	11.5	11.5

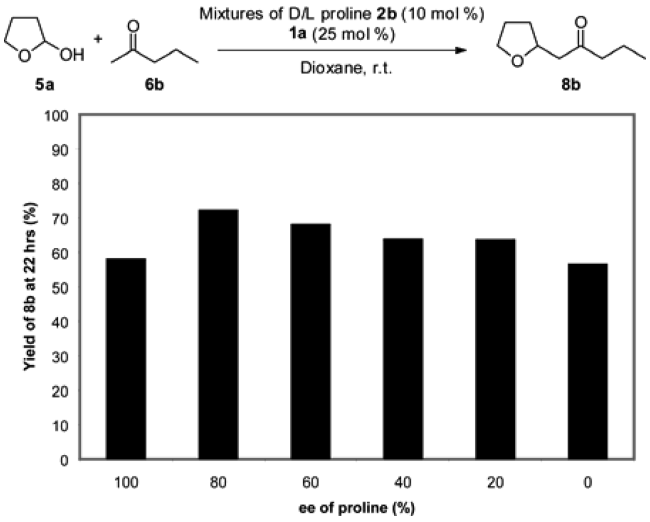
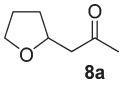


Figure 8. Yield of nonlinear effect reactions at 22 h.

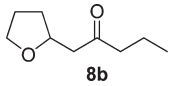
ketone (5.68 mmol, 5 equiv) is added. Proline derivative **2a** (0.114 mmol, 42.0 mg, 0.10 equiv) and urea **1f** (0.284 mmol, 106 mg, 0.25 equiv) are added. Upon complete consumption of starting material, as judged by GC analysis, silica gel was added to the reaction, solvent removed, and directly chomatographed using ethyl acetate/hexane mixtures to afford the desired compounds. Enantioselectivities were determined by chiral GC or HPLC analysis.



8a

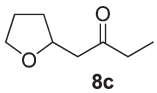
1-(Tetrahydrofuran-2-yl)propan-2-one 8a. Prepared according to a general procedure with dichloromethane as the solvent (due to high volatility of final product) using 113.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 4 h. The product was purified via flash chromatography on silica gel using 10% → 20% ethyl acetate/hexanes to give **8a** (65.9 mg, 40%) as a light yellow oil. R_f = 0.18 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.22 (m, J = 6.74 Hz, 1H), 3.86 (q, J = 7.34 Hz, 1H), 3.73 (q, J = 7.58, 1H), 2.75 (dd, J = 7.29, 15.87 Hz, 1H), 2.56 (dd, J = 5.55, 15.87 Hz, 1H), 2.19 (s, 3H), 2.10 (m, 1H), 1.89 (m, 2H), 1.47 (ddd, J = 10.43, 5.99, 18.26 Hz, 1H) ppm. ^{13}C NMR: (150 MHz, $DCCl_3$) δ 207.2, 75.0, 67.8, 49.6, 31.5, 30.6, 25.5 ppm. HRMS (EI+): calcd for $C_7H_{12}O_2$, 128.0837; found, 128.0831. The proton and carbon data were in accordance with those described in the literature.[32]

1-(Tetrahydrofuran-2-yl)pentan-2-one 8b. Prepared according to the general procedure using 502.4 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 h. The product was purified via flash chromatography on silica gel using 15% ethyl acetate/hexanes to give **8b** (719.8 mg, 81%) as a light



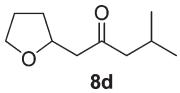
8b

yellow oil. R_f = 0.41 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ4.22 (m, J = 6.77 Hz, 1H), 3.86 (dd, J = 6.90, 15.06 Hz, 1H), 3.72 (dd, J = 7.33, 14.99 Hz, 1H), 2.73 (dd, J = 7.08, 15.78 Hz, 1H), 2.52 (dd, J = 5.82, 15.78, 1H), 2.43 (dt, J = 0.93, 7.37 Hz, 2H), 2.09 (td, J = 6.07, 19.76 Hz, 1H), 1.93–1.85 (m, 2H), 1.61 (m, J = 7.39 Hz, 2H), 1.46 (ddd, J = 10.44, 6.00, 18.30 Hz, 1H), 0.92 (t, J = 7.44 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ209.4, 75.1, 67.8, 48.6, 45.5, 31.5, 25.6, 17.0, 13.7 ppm. HRMS (ESI+): calcd for $[M + Na]^+$ $C_9H_{16}O_2Na$, 179.1043; found, 179.1046.



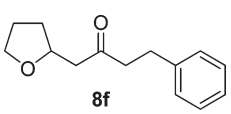
8c

1-(Tetrahydrofuran-2-yl)butan-2-one 8c. Prepared according to the general procedure using 106.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 6 h. The product was purified via flash chromatography on silica gel using 15% ethyl acetate/hexanes to give **8c** (133.0 mg, 78%) as an oil. R_f = 0.32 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ4.23 (m, J = 6.75 Hz, 1H), 3.86 (q, J = 7.32 Hz, 1H), 3.72 (q, J = 7.44, 1H), 2.74 (dd, J = 7.20, 15.72 Hz, 1H), 2.53 (dd, J = 5.73, 15.69, 1H), 2.47 (dq, J = 1.86, 2.42 Hz, 2H), 2.09 (m, 1H), 1.89 (m, 2H), 1.47 (ddd, J = 10.47, 6.00, 18.27 Hz, 1H), 1.05 (t, J = 7.29 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 75.2, 67.8, 48.3, 36.7, 31.5, 25.6, 7.6 ppm. HRMS (CI+): calcd for $C_8H_{15}O_2$, 143.1072; found, 143.1070.



8d

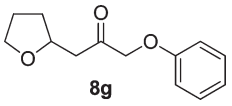
4-Methyl-1-(tetrahydrofuran-2-yl)pentan-2-one 8d. Prepared according to the general procedure using 100.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 8.5 h. The product was purified via flash chromatography on silica gel using 10% ethyl acetate/hexanes to give **8d** (132.5 mg, 69%) as an oil. R_f = 0.44 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.22 (m, J = 6.75 Hz, 1H), 3.85 (dd, J = 7.32, 14.64 Hz, 1H), 3.72 (dd, J = 7.41, 14.91 Hz, 1H), 2.73 (dd, 6.96, 15.90 Hz, 1H), 2.50 (dd, J = 5.91, 15.87 Hz, 1H), 2.33 (d, J = 7.08 Hz, 2H), 2.18–2.07 (m, J = 6.67 Hz, 2H), 1.92–1.86 (m, 2H), 1.46 (ddd, J = 10.14, 5.97, 18.30 Hz, 1H), 0.92 (d, J = 6.66 Hz, 6H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.1, 75.1, 67.8, 52.6, 49.1, 31.5, 25.6, 24.4, 22.6. 22.6 ppm. HRMS (CI+): calcd for $C_{10}H_{19}O_2$, 171.1385; found, 171.1389.



8f

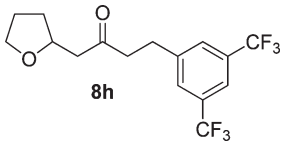
4-Phenyl-1-(tetrahydrofuran-2-yl)butan-2-one 8f. Prepared according to the general procedure using 111.5 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 h. The product was purified via flash chromatography on silica gel using 2% → 5% → 10% → 20% ethyl acetate/hexanes to give **8f** (208.8 mg, 76%) as an oil. R_f = 0.38 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 4.21 (m, J = 6.74 Hz, 1H),

3.84 (q, J = 7.32 Hz, 1H), 3.71 (q, J = 7.46 Hz, 1H), 2.90 (m, 2H), 2.79 (m, 2H), 2.72 (dd, J = 7.23, 15.75 Hz, 1H), 2.51 (dd, J = 5.61, 15.75 Hz, 1H), 2.07 (m, J = 6.40 Hz, 1H), 1.88 (m, 2H), 1.44 (ddd, J = 10.32, 5.97, 18.27 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ208.3, 141.1, 128.5, 128.3, 126.1, 75.1, 67.8, 48.9, 45.1, 31.5, 29.6. 25.6 ppm. HRMS (CI+): calcd for $C_{14}H_{19}O_2$, 219.1385; found, 219.1386. The proton and carbon spectra matched those previously reported.[33]



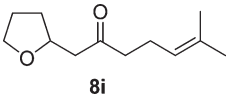
8g

1-Phenoxy-3-(tetrahydrofuran-2-yl)propan-2-one 8g. Prepared according to the general procedure using 113.0 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 22 h. The product was purified via flash chromatography on silica gel using a gradient of 5 → 10% ethyl acetate/hexanes to give **8g** (236.4 mg, 84%) as an oil. R_f = 0.33 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.99 (t, J = 7.35 Hz 1H), 6.89 (d, J = 8.58 Hz, 2H), 4.62 (q, J = 14.54 Hz, 2H), 4.29 (m, J = 6.86 Hz, 1H), 3.87 (q, J = 7.34 Hz, 1H), 3.74 (q, J = 7.44 Hz, 1H), 2.88 (dd, J = 7.44, 15.84 Hz), 2.71 (dd, J = 5.31, 15.87 Hz, 1H), 2.12 (m, J = 6.45 Hz, 1H), 1.91 (m, 2H), 1.52 (ddd, J = 10.41, 5.82, 18.12 Hz, 1H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 205.8, 157.8, 129.6, 121.7, 114.6, 74.8, 73.2, 67.9, 45.2, 31.6, 25.5 ppm. HRMS (CI+): calcd for $C_{13}H_{17}O_3$, 221.1178; found, 221.1163.



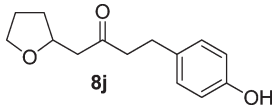
8h

4-(3,5-Bis(trifluoromethyl)phenyl)-1-(tetrahydrofuran-2-yl)-butan-2-one 8h. Prepared according to the general procedure using 110.3 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 12 h. The product was purified via flash chromatography on silica gel using a gradient of 5% → 20% ethyl acetate/hexanes to give **8h** (322.9 mg, 73%) as an oil. R_f = 0.41 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.71 (s, 1H), 7.65 (s, 2H), 4.20 (m, 1H), 3.84 (dd, J = 6.81, 15.21, 1H), 3.72 (dd, J = 7.62, 14.76 Hz, 1H), 3.09−3.00 (m, 2H), 2.93−2.82 (m, 2H), 2.70 (dd, J = 7.86, 15.24, 1H), 2.55 (dd, J = 4.95, 15.27 Hz, 1H), 2.07 (m, J = 6.39 Hz, 1H), 1.92−1.85 (m, 2H), 1.46 (ddd, J = 10.35, 6.03, 18.33 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ207.2, 143.6, 131.6 (q, J = 33.06), 123.4 (q, J = 272.56), 120.2 (m), 75.2, 67.9, 48.8, 44.0, 31.5, 28.9, 25.5 ppm. HRMS (CI+): calcd for $C_{16}H_{17}F_6O_2$, 355.1133; found, 355.1117.



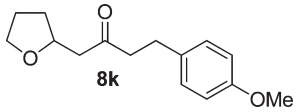
8i

6-Methyl-1-(tetrahydrofuran-2-yl)hept-5-en-2-one 8i. Prepared according to the general procedure using 109.3 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 h. The product was purified via flash chromatography on silica gel using a gradient of hexane, 2→10% ethyl acetate/hexanes to give **8i** (179.5 mg, 74%) as an oil. R_f = 0.48 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ5.06 (t, J = 7.14, 1H), 4.22 (m, J = 6.75 Hz, 1H), 3.85 (q, J = 7.36 Hz, 1H), 3.72 (q, J = 7.46 Hz, 1H), 2.73 (dd, J = 7.02, 15.84 Hz, 1H), 2.52 (dd, J = 5.76, 15.78 Hz, 1H), 2.48 (t, J = 7.32 Hz, 2H), 2.25 (q, J = 7.36 Hz, 2H), 2.09 (m, J = 6.39, 1H), 1.89 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.46 (ddd, J = 10.37, 5.93, 18.32, 1H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 209.1, 132.6, 122.8, 75.1, 67.8, 48.7, 43.6, 31.5, 25.6, 25.6, 22.3, 17.6 ppm. HRMS (ESI+): calcd for $C_{12}H_{20}O_2Na$ $[M + Na]^+$, 219.1356; found, 219.1347.



8j

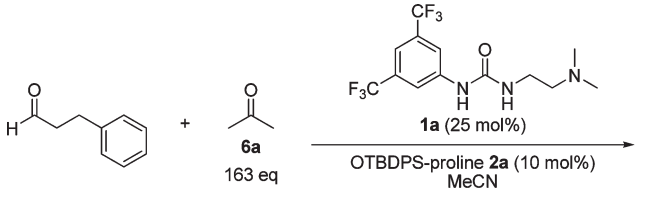
4-(4-Hydroxyphenyl)-1-(tetrahydrofuran-2-yl)butan-2-one 8j. Prepared according to the general procedure using 109.2 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 4.5 h. The product was purified via flash chromatography on silica gel using a gradient of 15% → 20% → 25% ethyl acetate/hexanes to give **8j** (230.1 mg, 79%) as an oil. R_f = 0.12 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.02 (m, 2H), 6.73 (m, 2H), 5.55 (s, 1H), 4.23 (m, J = 6.84 Hz, 1H), 3.85 (m, 1H), 3.73 (m, 1H), 2.82 (m, 2H), 2.73 (m, 3H), 2.51 (dd, J = 5.67, 15.81 Hz), 2.08 (m, 1H), 1.88 (m, 2H), 1.88 (m, 2.0H), 1.45 (ddd, J = 10.40, 5.93, 18.26 Hz, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 154.1, 132.9, 129.4, 115.3, 75.1, 67.8, 48.8, 45.3, 31.5, 28.7, 25.5 ppm. HRMS (CI+): calcd for $C_{14}H_{19}O_3$, 235.1334; found, 235.1335.

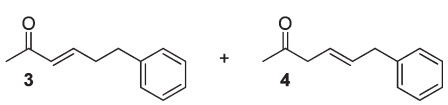


8k

4-(4-Methoxyphenyl)-1-(tetrahydrofuran-2-yl)butan-2-one 8k. Prepared according to the general procedure using 102.5 mg of 2-hydroxytetrahydrofuran. The reaction was stirred for 5 h. The product was purified via flash chromatography on silica gel using 5% → 10% → 20% ethyl acetate/hexanes to give **8k** (221.8 mg, 77%) as an oil. R_f = 0.29 in 30% ethyl acetate/hexanes. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.10 (m, 2H), 6.82 (m, 2H), 4.21 (m, J = 6.75 Hz, 1H), 3.78 (s, 3H), 3.71 (m, 1H), 2.84 (m, 2H), 2.73 (m, 3H), 2.50 (dd, J = 5.61, 15.75 Hz, 1H), 2.07 (m, 1H), 1.88 (m, 2H), 1.44 (ddd, J = 10.41, 6.03, 18.27 Hz, 1H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 208.5, 158.0, 133.1, 129.3, 113.9, 75.0, 67.8, 55.3, 48.9, 45.3, 31.5, 28.7, 25.6 ppm. HRMS (CI+): calcd for $C_{15}H_{21}O_3$, 249.1491; found, 249.1493.

■ ALDOL REACTION





Small-Scale Reaction Progress Plot. Proline derivative **2a** (4.06 mg, 0.010 mmol, 0.10 equiv) and urea **1a** (9.44 mg, 0.028 mmol, 0.25 equiv) were weighed into a 2 mL GC vial. Acetone (1.3 mL, 17.93 mmol, 163 equiv) was added to the vial.

The reaction was initiated with 220 μL of a stock solution containing 3-phenylpropionaldehyde (0.11 mmol, 220 μL, 0.05 M, 1 equiv) and mesitylene as an internal standard (0.011 mmol, 220 μL, 0.05 M, 0.10 equiv). The reactions were stirred at room temperature and directly sampled by GC for reaction progress. Products and starting materials are referenced to mesitylene.

Large-Scale Aldol Reaction. Proline derivative **2a** (35 mg, 0.094 mmol, 0.10 equiv) and urea **1a** (81 mg, 0.235 mmol, 0.25 equiv) were placed into a flask. Acetonitrile (1.9 mL) was added followed by acetone (11.2 mL, 153 mmol, 163 equiv). The reaction was initiated with 3-phenylpropionaldehyde (0.125 mL, 0.941 mmol, 1 equiv). The reaction was stirred at room temperature for 16 h. The reaction was then concentrated with silica gel and directly chromatographed using 2% diethyl ether/hexanes to afford the two observed products as light yellow oils.

Data for α,β Product ***3***. (37.5 mg, 92% purity assuming *t*-butyldiphenylsilanol as an impurity based upon comparison to previously reported spectrum,[34] 21% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.31−7.27 (m, 2H), 7.22−7.16 (m, 3H), 6.81 (dt, *J* = 6.81, 15.96 Hz, 1H), 6.09 (dt, *J* = 1.50, 15.96 Hz, 1H), 2.79 (t, *J* = 7.74 Hz, 2H), 2.58−2.51 (m, 2H), 2.22 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ198.5, 147.0, 140.7, 131.7, 128.5, 128.3, 126.2, 34.4, 34.1, 26.9 ppm. The proton and carbon data are in accordance with that reported in the literature.[35]

Data for β,γ Product ***4***. (36.4 mg, 22% yield). Exists as a ∼1:4.3 (*cis*:*trans*) mixture as judged by the peaks at 3.15 and 3.29 ppm. NMR data for the trans isomer are as follows. ^{1}H NMR: (600 MHz, $CDCl_3$) δ7.31−7.26 (m, 2H), 7.22−7.15 (m, 3H), 5.74−5.67 (m, 1H), 5.65−5.60 (m, 1H), 3.38 (d, *J* = 6.78, 2H), 3.15 (d, *J* = 6.66, 2H), 2.14 (s, 3H) ppm. ^{13}C NMR: (150 MHz, $CDCl_3$) δ 207.1, 140.1, 133.7, 128.52, 128.48, 126.1, 123.4, 47.4, 39.0, 29.44 ppm. The proton data are in accordance with that reported in the literature.[36]

■ ASSOCIATED CONTENT

Supporting Information. Copies of GC/HPLC chromatograms and corresponding chiral methods as well as ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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