JOC The Journal of Organic Chemistry

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Organocatalytic Enantioselective α-Hydroxymethylation of Aldehydes: Mechanistic Aspects and Optimization

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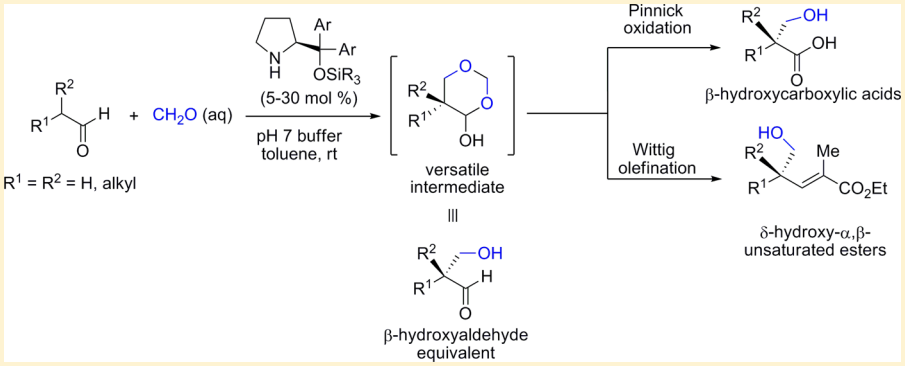
Supporting Information



ABSTRACT: Further studies of the direct enantioselective α-hydroxymethylation of aldehydes employing the α,α-diarylprolinol trimethylsilyl ether class of organocatalysts are described. This process has proven efficient for access to β-hydroxycarboxylic acids and δ-hydroxy-α,β-unsaturated esters from aldehydes in generally good yields, excellent enantioselectivity, and compatibility with a broad range of functional groups in the aldehyde. The goal of these studies was to identify the critical reaction variables that influence the yield and enantioselectivity of the α-hydroxymethylation process such as catalyst structure, pH of the medium, purity of the reactants and reagents particularly with respect to the presence of acidic impurities, and the nature of the buffer, along with the standard variables including solvent, time, temperature and mixing efficiency. The previously identified intermediate lactol has been further characterized and its reactivity examined. These studies have led to identification of the most critical variables translating directly into improved substrate scope, reproducibility, enantioselectivity, and yields.

INTRODUCTION

The efficient construction of complex molecules from simple and readily available starting materials remains a focal point in organic synthesis. As a result, the utilization of chiral building blocks at early stages in a synthesis is often desirable in an effort to develop a highly branched and thus more efficient approach to the desired target. Among this array of building blocks, α-substituted β-hydroxyaldehydes and carboxylic acids have demonstrated their utility in the synthesis of a variety of complex molecules.[1−4]

The most common routes for the preparation of α-substituted β-hydroxyaldehydes and carboxylic acids have utilized chiral auxiliary based enolate chemistry such as those originally developed by Evans.[5,6] While these methods are effective in furnishing the desired molecules in high yield and stereoselectivity, the process usually requires multiple synthetic operations including the introduction and removal of the auxiliary utilized as well as the employment of an equivalent of formaldehyde in gaseous form or the formaldehyde equivalent, benzyl chloromethyl ether, as the alkylating reagent. In addition, these methods require recycling of stoichiometric amounts of chiral auxiliary limiting their practicality upon scale-up. As a result, a single step, readily scalable method for the generation of these synthons would be highly desirable.

Over the course of the past decade, synthetic organic chemists have begun to address the aforementioned limitations of auxiliary based methods through applications of catalysis, including organocatalysis.[7−11] These methods have become particularly useful for α-functionalization reactions of aldehydes catalyzed by chiral secondary amines, and have been shown to be effective for a broad range of electrophiles and nucleophiles. The advantage of this approach is that one can enantioselectively generate a new stereocenter at the α-position of an aldehyde in a single step using only a catalytic quantity of the chiral catalyst under mild, often near neutral conditions. Furthermore, unlike some auxiliary based methods, the chiral catalyst can often be recovered during the workup and reused. One of the most prominent applications of organocatalysis, beginning with the pioneering work by List, Lerner, and Barbas,[12] has been to intermolecular aldol reactions.[13−15]

However, in the case of intermolecular crossed aldol reactions employing the powerful C_1 synthon formaldehyde,

Received: February 17, 2015
Published: March 20, 2015

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

only a limited number of such transformations have been reported, primarily employing transition metal based Lewis acid catalysts. Ito and co-workers performed an α-hydroxymethylation on 2-cyanopropionate derivatives with formaldehyde catalyzed by a Rh(I)-TRAP complex.[16,17] Sodeoka and co-workers described an asymmetric α-hydroxymethylation of β-keto esters with formaldehyde catalyzed by a Pd(II)-BINAP complex,[18] while similarly Shibasaki and co-workers developed a related reaction employing a Ni(II)-Schiff base complex as catalyst.[19] In addition, α-hydroxymethylation has been performed on silyl enol ethers by Yamamoto and co-workers mediated by a AgOTf-BINAP complex,[20] and by Kobayashi and co-workers employing a chiral scandium complex.[21] Although these methods provided useful levels of enantioselectivity, we sought to pursue a simpler, more practical and scalable method for the enantioselective α-hydroxymethylation of aldehydes.

Others workers also realized the potential utility of such an enantioselective organocatalytic crossed aldol reaction with formaldehyde. In 2004, Córdova and co-workers described the use of L-proline to catalyze the enantioselective α-hydroxymethylation of a limited number of aliphatic aldehydes in moderate yields and reportedly exceptionally high enantioselectivity (>99%).[22] However, we and others have been unable to reproduce the reported levels of enantioselectivity. In our hands, isovaleraldehyde reproducibly afforded only 70% ee under the reported reaction conditions. In 2006, Pihko and co-workers reported an organocatalytic α-methylenation of aldehydes under catalysis by amine salts including chiral amine salts of acids.[23] This study may have been initially targeting α-hydroxymethylation, but that result could not be obtained without concomitant elimination of water under the acidic conditions employed.

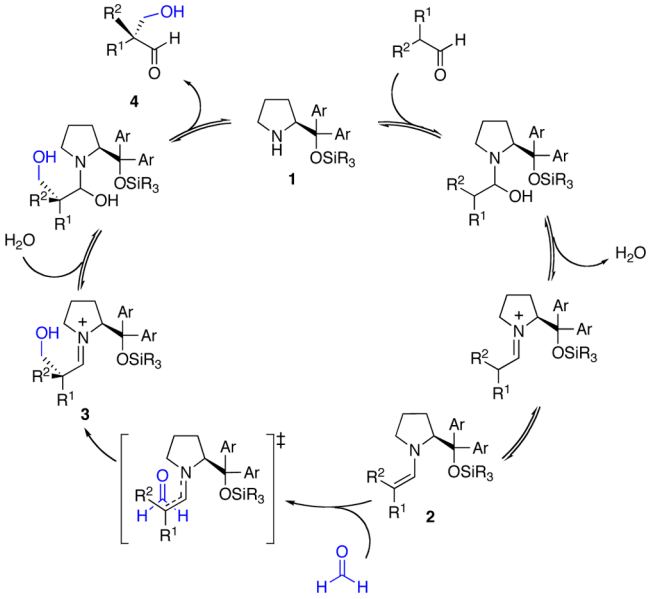
In 2009, our laboratory reported an alternate protocol catalyzed by α,α-diphenylprolinol trimethylsilyl ether.[24] This class of catalysts, first reported by Jørgensen[25] and Hiyashi,[26] has been utilized for a variety of α-functionalization reactions of aldehydes.[27−30] Our studies defined an experimental protocol for enantioselective α-hydroxymethylation which was demonstrated to be readily scalable and general across a number of functionalized aldehydes. More recently, Hayashi and co-workers have reported a related enantioselective α-hydroxymethylation of aldehydes catalyzed by the related 3,5-bistrifluoromethylaryl prolinol in comparable yields and enantioselectivity, but with the opposite sense of asymmetric induction.[31] In contrast to our protocol, where the enantioselectivtiy is apparently controlled by the steric bulk of the diaryl- and trialkylsilyloxy- substituent of the prolinol, the catalyst systems employed by Córdova and Hayashi apparently impart enantioselectivity through hydrogen bonding with the carboxylic acid or alcohol functionality of the catalyst serving to orient the formaldehyde electrophile *syn* to the α substituent of the proline in the transition state.[32,33]

To better understand the controlling reaction variables of our protocol, we have undertaken a more in-depth study of the these variables, such as reactant and catalyst purity, catalyst structure, pH of the reaction medium, source of formaldehyde, methods of buffering, solvent polarity, and stirring rates. We have also further characterized the intermediate lactol, and studied the chemical and configurational stability and reactivity of this intermediate.[24]

RESULTS AND DISCUSSION

Establishing A Feasible Catalytic Cycle. The originally postulated mechanism of the α-hydroxymethylation is common to other organocatalytic aldol reactions.[12−15] Condensation of the diaryltrialkylsilyloxy prolinol catalyst **1** with an aldehyde generates an equilibrium concentration of enamine **2**. Subsequent attack of enamine **2** on formaldehyde occurs from the less hindered *si* face of the enamine, as the *re* face is blocked by nonbonding steric interactions from the sterically demanding α-substituent of the catalyst **1**. Hydrolysis of the resulting iminium ion (**3**) results in α-hydroxymethylated product **4** (Scheme 1).

Scheme 1. Postulated Catalytic Cycle for Enantioselective α-Hydroxymethylation Catalyzed by 1

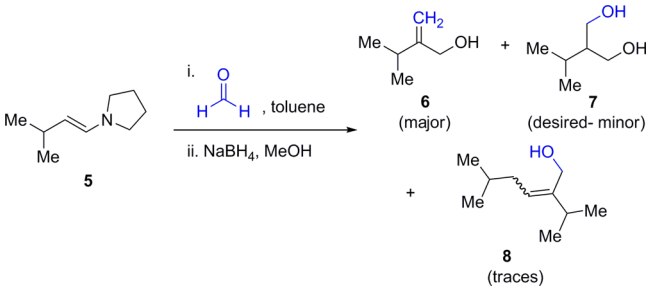


To investigate the feasibility of the foregoing catalytic cycle, we began with the reaction of the preformed enamine **5**, derived from pyrrolidine and isovaleraldehyde with varying amounts of 37% aq formaldehyde (formalin).[32] Our preliminary experiments demonstrated that use of ∼3.0 equiv of formalin in a variety of solvents followed by the reduction of crude products with sodium borohydride ($NaBH_4$) provided substantial amounts of allylic alcohol **6**[33] rather than the desired α-hydroxymethylation product **7**[22] accompanied by trace amounts of alcohol **8** derived from the self-condensation of isovaleraldehyde followed by dehydration (1.5:1:trace of **6**:**7**:**8**).[34] However, we noted variability in the product distribution depending on the sample of commercial formalin used. Given the known propensity of formaldehyde to undergo oxidation to formic acid over time, we measured the pH of the samples of commercial formalin used and found that they ranged from pH 3−5. We thus postulated that the formation of the undesired elimination product **6** was due to the presence of formic acid. Indeed, Pikho and co-workers reported a similar observation during their studies of the α-methylenation of aldehydes.[23] Upon the basis of this observation, an attempt was made to buffer the reaction medium. Gratifyingly, we discovered that buffering the reaction medium with commercially available solid pH 7 phosphate buffer almost completely suppressed the formation of elimination product **6** and gave

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

predominantly the desired diol **7** (1:12 **6**:**7**) as shown in Scheme 2.

Scheme 2. Preliminary Experiments with Enamine 5



With a workable source of formaldehyde identified, we then focused on optimizing the concentration of the reaction. We determined that running the reaction at a concentration of 0.5 M completely suppressed the formation of dimer **8**. While the desired α-hydroxymethylation occurred in a variety of different solvents, we observed significantly better yields with nonpolar solvents that were immiscible with formalin including toluene, hexane, DCM, and chloroform. We were pleased to find that using a catalytic amount of pyrrolidine (20−30%) the desired α-hydroxymethylation occurred in the biphasic medium in ∼12 h affording the expected diol in good yield (after reduction with $NaBH_4$). Attempts to decrease the catalyst loading, while successful, led to inconveniently long reaction times in these initial experiments.

Once a catalytic cycle for α-hydroxymethylation was demonstrated with pyrrolidine, we then set out to explore the asymmetric variant. Our chosen catalyst class was the Jørgensen−Hayashi diarylprolinol derived catalysts. Although commercial sources of some of these catalysts are available, we found that the commercial samples afforded inconsistent results as the result of the presence of unknown impurities, which were difficult to remove in our hands (vide infra). Thus, we chose to prepare these materials to ensure reproducibility.

Our catalyst preparation, shown in the context of the synthesis of (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-pyrrolidine (**13**), began with esterification of commercially available *N*-Boc-L-proline (**9**) producing the corresponding methyl ester **10**. The addition of two equivalents of phenylmagnesium bromide (PhMgBr) reagent in THF to ester **10** provided *N*-Boc-L-diphenylprolinol **11**. The Boc group was then removed by treatment with sodium hydroxide (NaOH) in ethanol (EtOH) at reflux to give diphenylprolinol **12**. Finally, protection of the hydroxyl function with trimethylsilyl triflate afforded target catalyst **13** (Scheme 3).

It should be noted that this route is readily scalable and produces material of equal spectroscopic purity (^1H NMR, ^{13}C NMR) and physical appearance in comparison to the commercial catalyst (see Figure 1) and has been broadly

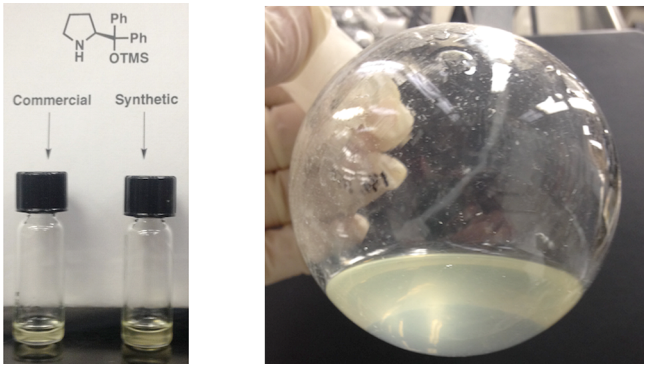


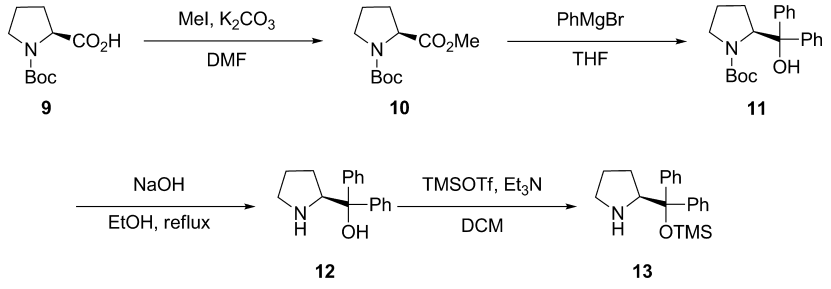
Figure 1. Commercial vs synthetic (*S*)-2-(diphenyl((trimethylsilyl)-oxy)methyl)pyrrolidine (25 g scale batch).

applied to synthesize all derivatives used in our study. While all steps are high yielding and the route can be performed without purification until after silylation, we found that it is critical to recrystallize prolinol intermediate **12** prior to silylation in order to ensure high yields and enantioselectivities in the ensuing α-hydroxymethylation reactions.

Establishing An Enantioselective Catalytic Cycle. We began our investigation of the asymmetric variant of the α-hydroxymethylation process by initially investigating the reaction of isovaleraldehyde **14** with diarylprolinol silyl ether **13** in a biphasic mixture of toluene and ∼3.0 equiv of formalin containing a commercial solid phosphate buffer (Scheme 4). Quite unexpectedly, we obtained what we later determined to be the cyclic lactol **15** derived from the expected β-hydroxyaldehyde by incorporation of an additional equivalent of formaldehyde. As we reported earlier, we attributed the excellent enantioselectivity observed (vide infra) to the rapid formation of **15**. We surmised that closure to the cyclic acetal may serve to prevent potential racemization of the newly generated stereocenter via one or more of several conceivable pathways.[24]

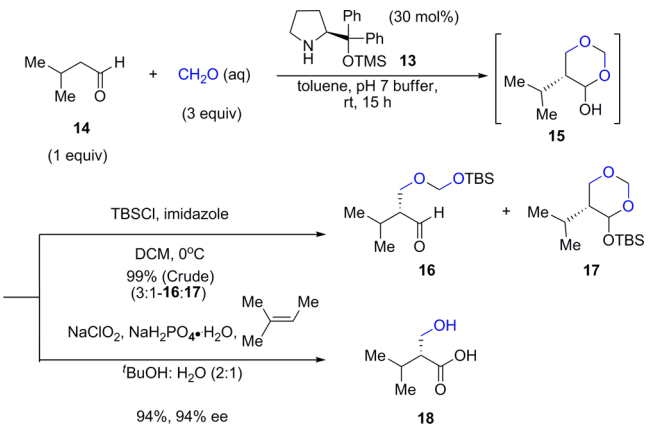
Initial attempts to handle and purify lactol **15** did not prove fruitful, thus we concluded that either protection of the lactol or transformation to a more stable derivative by, for example, oxidation would readily provide configurationally stable, isolable materials suitable for further transformations. The structure of the intermediate lactol **15** was originally inferred from the formation of the silyl protected aldehyde **16** upon treatment of crude lactol with TBSCl/imidazole. A subsequent,

Scheme 3. Preparation of the Jørgensen−Hayashi Prolinol Catalysts



DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

Scheme 4. Enantioselective Hydroxymethylation of Isovaleraldehyde (14)



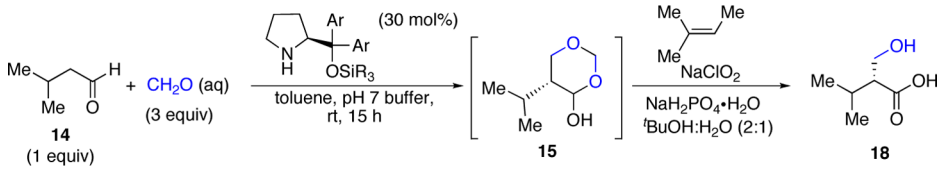
more detailed examination of the silylation reaction revealed that the product is actually a mixture of silyl protected aldehyde **16** and the corresponding TBS protected lactol **17**, which have proven challenging to separate via a variety of purification methods. As was previously reported, the resulting silyl protected aldehyde **16** proved too sensitive to racemization to allow purification by flash chromatography.[24] However, the mixture of **16** and **17** was obtained pure enough for further use of the protected aldehyde as a synthetic equivalent of chiral α-hydroxymethyl isovaleraldehyde.[24] Alternatively, Pinnick oxidation ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene) of the intermediate lactol **15** afforded desired (*R*)-2-(hydroxymethyl)-3-methylbutanoic acid (**18**) in excellent yield (94%) and enantioselectivity (94% ee) as depicted in Scheme 4.

Optimization Studies: Catalyst Structure and Loading. We initiated our optimization efforts by examining the effects of modifying the steric and electronic properties of diphenylprolinol catalyst **13** that was employed in our initial studies. We screened a series of derivatives of **13** with varying aryl groups in the catalytic α-hydroxymethylation of isovaleraldehyde (**14**) under identical reaction conditions. For this substrate, we observed that original catalyst **13** (Ar = Ph, R′ = CH_3) was superior in providing the desired β-hydroxy acid **18** in excellent yield and enantioselectivity (94% yield, 94% ee). The trends discernible from the data in Table 1 demonstrate that as the size of the aryl group and/or the silyl protecting group increases, it generally leads to a more sluggish reaction. Furthermore, we found that increasing the electron density in the aryl rings was tolerated, whereas utilizing catalyst **22** (Ar = 3,5-$(CF_3)_2$Ph, R′ = CH_3) bearing electron deficient aryl groups (Table 1, entry 4), resulted in no conversion. We postulate that, in this case, the catalyst is sufficiently nonbasic and/or non-nucleophilic that either the rate of enamine formation is slowed or the equilibrium concentration of the intermediate enamine is too low to sustain a reaction rate observable over the time scale employed. Alternatively, it is also possible that the enamine intermediate generated from condensation with **14** is insufficiently nucleophilic to perform α-hydroxymethylation at an observable rate on the time scale employed. However, the successful application of the free alcohol analogue of this catalyst to enantioselective α-hydroxymethylation by Hayashi suggests that the former rather than the latter rationale may be more plausible.[31] It should also be noted that the reaction was run with a commercial sample of catalyst **13** (Table 1, entry 12) and the results were comparable in this case (89% yield, 91% ee). However, for this case, in our hands there was significant variability in yield and enantioselectivity, sample to sample, for different commercial samples of catalyst **13**.

We also examined the effects of catalyst loading. We were pleased to see the reaction perform with consistent yield and enantioselectivity at as low as 5 mol % catalyst loading at constant reactant concentration (0.5 M of substrate in toluene) although at the expense of ~4−5-fold increase in the time required for full conversion.

Optimization Studies: The Solvent. Having established a reliable set of partially optimized biphasic reaction conditions, we next examined whether the nature of organic solvent affected the observed enantioselectivities and yield. The results of these solvent screening studies are outlined in Table 2.

Table 1. Screening Catalysts for α-Hydroxymethylation



entry	cat #	-Ar	-SiR_3	mol % cat	yield (%)	ee (%)
1	**19**	4-(OMe)Ph	-$SiMe_3$	30	75	89
2	**20**	4-(F)Ph	-$SiMe_3$	30	81	95
3	**21**	3,5-$(Me)_2$Ph	-$SiMe_3$	30	72	93
4	**22**	3,5-$(CF_3)_2$Ph	-$SiMe_3$	30	n.r.	n.r.
5	**23**	2-naphthyl	-$SiMe_3$	30	61	93
6	**13**	Ph	-$SiMe_3$	30	94	94
7	**24**	Ph	-$SiEt_3$	30	86	94
8	**25**	Ph	-$SiMePh_2$	30	69	96
9	**13**	-Ph	-$SiMe_3$	20	89	93
10	**13**	-Ph	-$SiMe_3$	10	91	95
11	**13**	-Ph	-$SiMe_3$	5	95	92
12	**13**[a]	-Ph	-$SiMe_3$	30	89	91

[a]Commercial sample of catalyst.

DOI: 10.1021/acs.joc.5b00380
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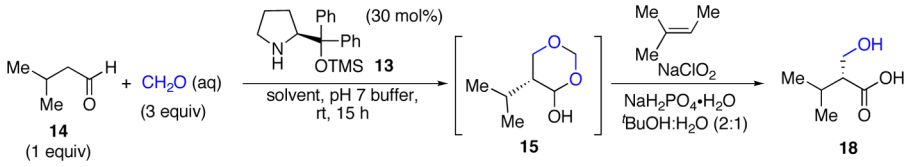
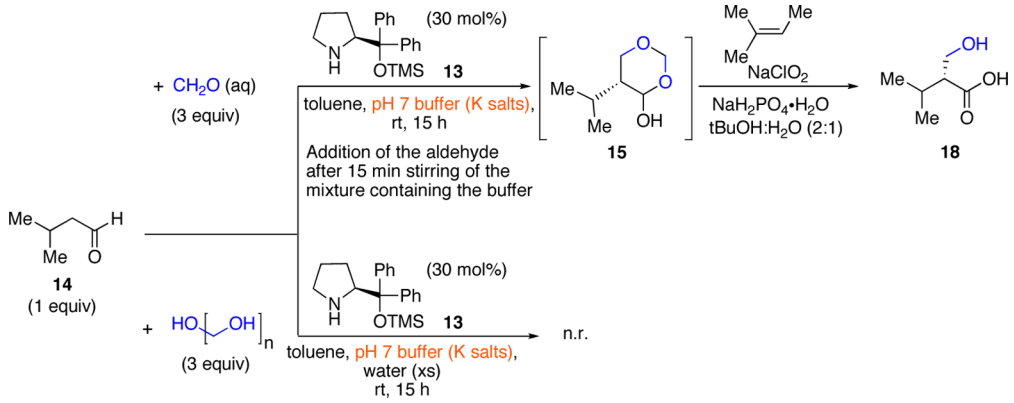
Table 2. Solvent Effects on α-Hydroxymethylation Yield and Enantioselectivity



entry	solvent	yield (%)	ee (%)
1	toluene	91	94
2	hexanes	69	97
3	EtOAc	59	86
4	Et_2O	63	93
5	THF	44	70
6	CH_2Cl_2	38	87
7	$CHCl_3$	38	87
8	DMF	n.r.	n.r.

Scheme 5. Evaluation of Formalin vs Paraformaldehyde Using the Optimal pH 7 Buffer



As can be seen from these results, we observed that the reaction generally performed well in nonpolar solvents (hexanes, toluene) as well as in ethyl acetate (EtOAc). It should be noted that the lower yields obtained in hexanes and EtOAc can be primarily attributable to slower conversion (~60−70% after 15 h) and that, for all these solvents, only traces of elimination products were observed. However, we found that chlorocarbon solvents (DCM, and chloroform), still afforded high enantioselectivity (87% ee); however, the yield of α-hydroxymethylation product suffered owing to byproduct formation via competing acid catalyzed elimination.

When THF was employed as solvent, large quantities of elimination product along with a major decrease in enantioselectivity (70% ee) were observed. The polarity of THF is not markedly different from the solvents that afforded high enantioselectivity, thus we tentatively attribute these effects to the increased miscibility of THF and formalin.

Optimization Studies: The Source of Formalin and the Nature of the Buffer. Thus far in our studies, the primary competing process observed has been elimination of water from the primary product, the β-hydroxy aldehyde, or a related intermediate. This issue was identified during our original study.[24] At that time, we had postulated that the elimination was occurring as a result of the presence of acid in the reaction medium, likely from variable amounts of formic acid present in the commercial samples of formalin employed. To overcome this problem, the α-hydroxymethylation reaction was performed in the presence of commercial pH 7 buffer salts, a mixture of dibasic sodium phosphate and monobasic potassium phosphate (Certified pH 7.00 ± 0.02 at 25 °C). This modification immediately afforded dramatically improved results for isovaleraldehyde (**14**), our test case, affording 94% yield, and 94% enantioselectivity, with no formation of the byproduct from competing elimination (Scheme 5). While we were delighted with this result, during our further studies it was found that this buffering procedure was not entirely reliable or broadly applicable across a broad range of structurally varied aldehyde substrates.

Thus, we felt it was necessary to examine the effects of the choice of the buffer salts on the yield and enantioselectivity of the α-hydroxymethylation process. We performed the same series of experiments with different freshly prepared pH 7 buffer salts. These included buffers derived only from sodium salts (monobasic sodium phosphate and dibasic sodium phosphate), the commerical mixtures of sodium and potassium salts, and only potassium salts (monobasic potassium phosphate and dibasic potassium phosphate). The results observed for the buffer containing only sodium salts mirrored those of the mixtures of sodium and potassium salts present in commercial as well as freshly prepared buffers comprising sodium/potassium salt mixtures. The results were not entirely reproducible or general across a range of aldehyde substrates. However, when a freshly prepared mixture of pH 7 buffer salts containing only potassium salts was employed, it was found that the reaction not only performed well with the isovaleraldehyde (**14**) test case, but across a wide variety of substrates (Scheme 5) as will be discussed in more detail below. We attribute these observations to the observed increase in solubility of the pH 7

DOI: 10.1021/acs.joc.5b00380
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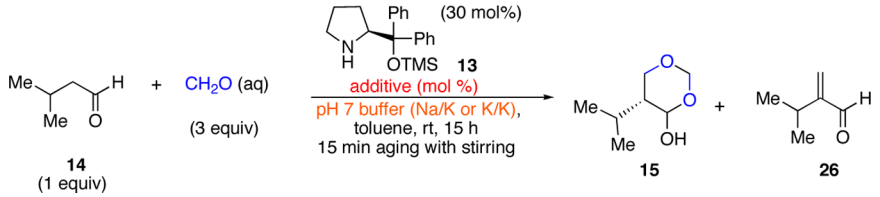
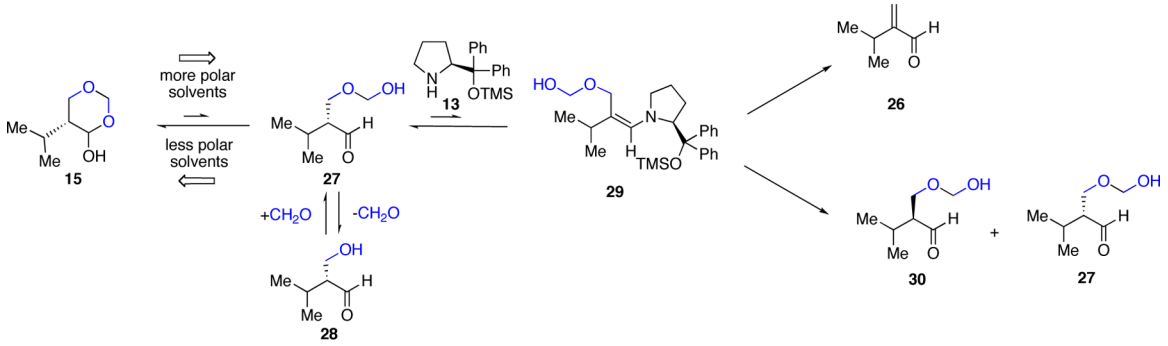
Table 3. Additive Effects in the Production of Lactol 15



entry	additive (mol %)	buffer salts	ratio of products (15:26)
1	NaOAc (10)	Na/K	99:1
2	AcOH (10)	Na/K	50:50
3	isovaleric acid (10)	Na/K	1:99
4	isovaleric acid (0.1)	Na/K	95:5
5	isovaleric acid (10)	K/K	1:99
6	isovaleric acid (0.1)	K/K	99:1

Scheme 6. Racemization, Elimination, or Loss of Formaldehyde from Lactol 15



buffer salt mixture derived from only potassium salts in the reaction mixture, which resulted in better apparent buffering capacity. Furthermore, we determined that addition of the buffer salts to the reaction mixture containing the catalyst, formalin, and toluene and stirring for 15 min prior to addition of the aldehyde substrate resulted in the most reliable, efficient formation of the intermediate lactol **15**.

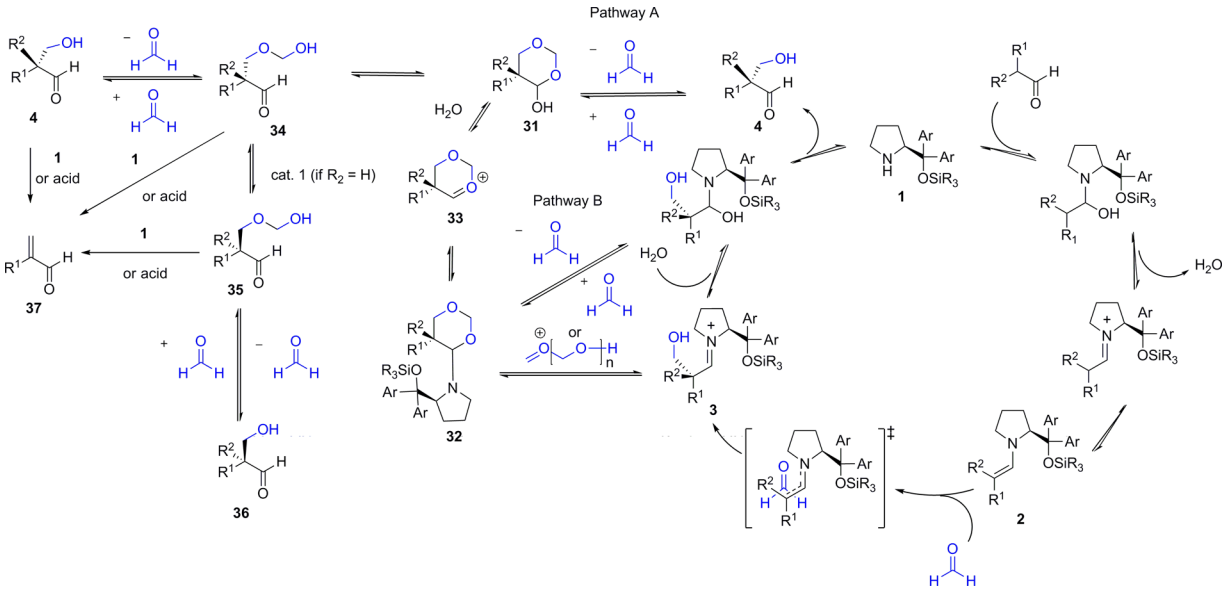
We also observed that the age of the formalin reagent was a variable. On one occasion, when an old (unknown age, potentially years old) sample of commercial formalin was utilized, the yield suffered dramatically. We speculated that this sample had largely been converted to paraformaldehyde and/or formic acid. In light of this observation, we attempted use of paraformaldehyde in aq buffered biphasic toluene/water medium and observed no observable reaction. Apparently, paraformaldehyde does not undergo appreciable dissociation to monomeric formaldehyde (or its hydrate) under these reaction conditions, and is thus not suitable for use in the catalytic α-hydroxymethylation process (Scheme 5). Thus, use of fresh samples of commercial formalin (stabilized by 10−15% methanol) should be employed to obtain optimal results.

Optimization Studies: Purity of the Aldehyde Substrates. During more detailed studies of the reaction variables, another significant observation was made: no competing elimination occurred when the substrate aldehydes were freshly purified by distillation or chromatography. We began to consider the possibility that the corresponding acid, presumably resulting from air oxidation of the aldehyde was promoting elimination. To test this hypothesis, reactions were run in which substoichiometric quantities of acetic acid (AcOH) and sodium acetate (NaOAc) were added to the reaction mixture under the standard reaction conditions using the commercial Na/K salt buffer. The addition of 10 mol % of AcOH led to a significant amount of elimination product **26**, while the addition of NaOAc had no effect on the formation of the intermediate lactol **15**. The reaction was then conducted in the presence of varying amounts of isovaleric acid, the organic acid derived from the substrate isovaleraldehyde (**14**). We found that the presence of as little as 0.1 mol % of acid present can lead to formation of small amounts of elimination product **26**. Subsequently, we determined that use of the K salt buffer suppresses elimination in the presence of 0.1 mol % of isovaleric acid, but elimination product **26** is still observed when 10 mol % of isovaleric acid is present. These results indicate that use of purified aldehydes in the presence of the K salt buffer provides optimal results in the α-hydroxymethylation process (Table 3).

Optimization Studies: Structure and Reactivity of the Intermediate Lactol 15. Considering our results in total so far, we still found it puzzling that an apparently tiny amount of acid impurity in the aldehyde substrate was sufficient to promote observable amounts of elimination product **26**, particularly when the commercial pH 7 Na/K buffer was utilized. Further consideration of the mechanistic pathway leading to elimination led us to question what intermediate was actually responsible for generation of the elimination product **26**. Monitoring the reaction in toluene, we observed the presence of equilibrium between the open and closed forms, lactol **15** and hydroxy aldehyde **27**, in favor of the closed form **15** (**15**:**27** ratio 3:1) as shown in Scheme 6. While monitoring the same reaction during the previously described solvent screen, we observed that the equilibrium between **15** to **27** shifted toward the open form aldehyde **27** in solvents that had not performed well in the α-hydroxymethylation reaction.

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

Scheme 7. Detailed Catalytic Cycle for Enantioselective α-Hydroxymethylation of Aldehydes



Thus, we envisioned the following mechanistic scheme to account for all of our observations. When significant amounts of the open form hydroxy aldehyde are present, as is the case in more polar solvents, the catalyst **13** may form the enamine **29** derived from **27** leading to partial or complete racemization to a mixture enantiomeric hydroxy aldehydes **27** and **30** and/or elimination to aldehyde **26** after hydrolysis (Scheme 6).

Another trend we observe is illustrated in Scheme 6. We also observe formation of minor amounts of another aldehyde, tentatively assigned as hydroxymethyl aldehyde **28** that we attribute to the loss of one equivalent of formaldehyde from aldehyde **27**. Minimally, the presence of an additional equivalent of formaldehyde completely suppresses the formation of **28**.

Formulation of the Complete Catalytic Cycle. Taking into account all of the data obtained from the foregoing studies, we are now able to formulate a more detailed description of the catalytic cycle including the potential formation of elimination products. As described in our original work, enamine catalysis from starting aldehyde to α-hydroxymethylated aldehyde **4** follows the typical pathway.[24] The formation of the observed lactol **31** could occur via initial formation of aldehyde **4** followed by rapid consumption of an additional equivalent of formaldehyde and cyclization to furnish **31** (Scheme 7, Pathway A). Alternatively, reaction of intermediate **3** or the derived aminol with a second equivalent of formaldehyde could also occur leading to formation of **31**. Another possibility could arise from addition of a second equivalent of formaldehyde in the form of its mono-, di-, or oligomeric oxonium ion to α-hydroxymethylated iminium species **3**. Subsequent ring closure to aminal **32**, departure of aminocatalyst **1** giving oxonium ion **33**, and finally quenching with water generates lactol **31** (Scheme 7, Pathway B). On the basis of our experiments, we hypothesize that further reactions of lactol **31** are under thermodynamic control. Lactol **31** is in equilibrium with the corresponding ring-opened aldehyde **34** (3:1 ratio in toluene). Changes in this equilibrium ratio are primarily based on pH and polarity of solvent. When the pH of the medium is acidic, this encourages the equilibrium between **31** and **34** to shift toward **34**, allowing for condensation of catalyst with aldehyde **34**, leading to either racemization (**34** and its enantiomer **35**) and/or subsequent elimination to furnish unsaturated aldehyde **37**. Of course, additional possibilities also exist such as loss of a proton from **3** (R^2 = H to form the related enamine) followed by nonstereoselective reprotonation to give **4** and **36** or by loss of water to form a conjugated iminium ion and hydrolysis to **37**.

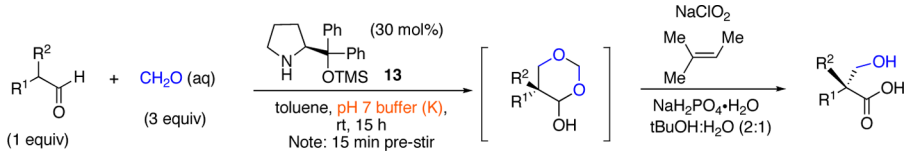
When the pH is neutral and the medium is nonpolar, the equilibrium favors lactol **31** which is sufficiently configurationally stable to (1) be transformed into isolable synthons, and (2) to prevent racemization by blocking further condensation of catalyst, amine **1**. In light of this analysis, one can conclude that all the equilibrium constants must strongly favor lactol **31** when excess formaldehyde is present. We also suggest that the optimal conditions arise from the requirement for the presence of at least one additional equivalent of formaldehyde, which serves to (1) ensure that there is excess formaldehyde present to drive the equilibrium to lactol **31** from **4**, and (2) possibly also to sequester the catalyst after the completion of the reaction (Scheme 7).[23]

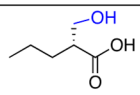
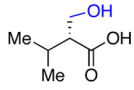
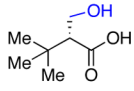
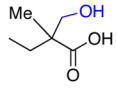
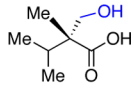
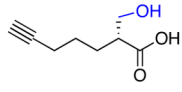
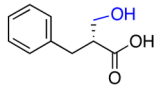
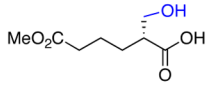
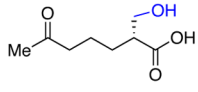
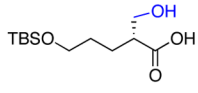
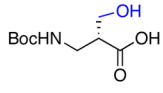
Once the optimal reaction conditions had been determined, we began to further examine the scope of this process with respect to the aldehyde. We sought to extend the scope even more broadly than in our preliminary studies.[24] We chose a group of structurally diverse aldehydes as shown in Table 4. We found that the reaction performed well across a variety of branched aliphatic aldehydes such as **18**, and **38**–**41** (Table 4, Entries 1–5).

We generally found that as the β-branching of the aldehyde increases, the reaction becomes increasingly sluggish, likely due to steric hindrance by the β branches impeding either formation of the required enamine, or perhaps more plausibly, reaction with formaldehyde. This proposal was further supported in the cases of substrates with α-branching, which required refluxing conditions to promote α-hydroxymethylation. In our original study we had reported that α-hydroxymethylation of 2-methylbutyraldehyde provided the expected acid **40** (after oxidation) bearing a quaternary center with very high enantioselectivity (Table 4, entry 4).[24] Upon re-examination of this reaction, it was determined that our

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030–4045

Table 4. Scope of Aldehydes for Enantioselective α-Hydroxymethylation−Pinnick Oxidation

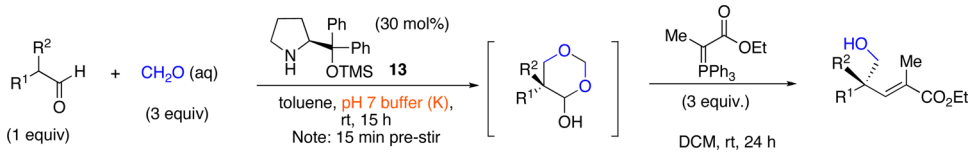


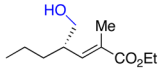
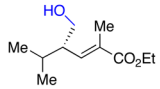
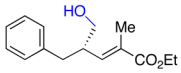
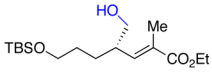
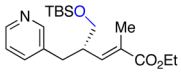
entry	product	reaction time (h)	temperature	yield (%)	ee (%)
1	 **38**	15	rt	94	93
2	 **18**	15	rt	94	94
3	 **39**	120	rt	69	90
4	 **40**	24	reflux	78	0
5	 **41**	68	reflux	36	19
6	 **42**	12	rt	68	91
7	 **43**	15	rt	95	92
8	 **44**	20	rt	91	88
9	 **45**	15	rt	87	96
10	 **46**	15	rt	94	93
11	 **47**	30	rt	65	91

analytical method had failed to separate the two enantiomers during the determination of the % ee. In fact, the reaction proceeds with no observable enantioselectivity. However, as the difference in the steric demand of the two groups at the reacting center increases as is the case for 2,3-dimethylbutyraldehyde, the resulting acid **41** (Table 4 Entry 5) exhibits a low but not practically useful level of enantioselectivity (19% ee).

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

Table 5. Substrate Scope for Tandem α-Hydroxymethylation−Wittig Olefination



entry	product	reaction time (h)	temperature	yield (%)	ee (%)
1	 **48**	15	rt	88	90
2	 **49**	15	rt	87	90
3	 **50**	15	rt	89	84
4	 **51**	15	rt	94	86
5	 **52**	48	rt	52 (3 steps)	83

The evaluation of functional groups including protecting group compatibility with the conditions required for α-hydroxymethylation were also studied. We were pleased to find that a variety of functional groups including some common protecting groups were tolerant of the reaction conditions. The functional groups that tolerated the α-hydroxymethylation−oxidation sequence and provided the desired chiral α-hydroxymethyl acids **42**−**47** in generally very good to excellent yields and % ee included a terminal alkyne, aryl group, methyl ester, ketone, TBS protected alcohol, and Boc protected amine (Table 4, entries 6−11). Particularly noteworthy is the completely regioselective α-hydroxymethylation of an ω-keto-aldehyde to afford keto acid **45** in 87% yield and 96% ee.

To extend the utility of the enantioselective α-hydroxymethylation, we wanted to highlight the versatility of the intermediate lactol. Attempts to selectively protect the open form of the intermediate lactol **15** did not achieve optimal results affording only moderate selectivity (3.5:1 **16**:**17**) employing a variety of silylating agents and reaction conditions. Therefore, we shifted our focus to employing the lactol **15** directly since we had demonstrated that the lactol **15** was in equilibrium with the requisite hydroxy aldehyde intermediate. Presumably by employing reactions that would selectively transform the aldehyde isomer in situ, the resulting shift in the equilibrium between lactol and aldehyde forms would allow complete conversion of lactol **15** to the requisite product(s).

To this end, we discovered that treatment of the intermediate lactols derived from five substrates, four of which had been examined in Table 4, with ethyl 2-(triphenylphosphoranylidene)propanoate, afforded the corresponding δ-hydroxy-α,β-unsaturated esters in high yield and stereoselectivity (Table 5). An example of this type of tandem process has also recently been reported by Hayashi and co-workers, employing a different stabilized ylide.[31]

While we were pleased with the substrate scope of the α-hydroxymethylation, some limitations have been encountered thus far. Substrates with the general structures **53**−**56** did not undergo α-hydroxymethylation under the optimized reaction conditions (Figure 2). For **53**, we suspect that the low reactivity

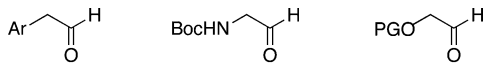


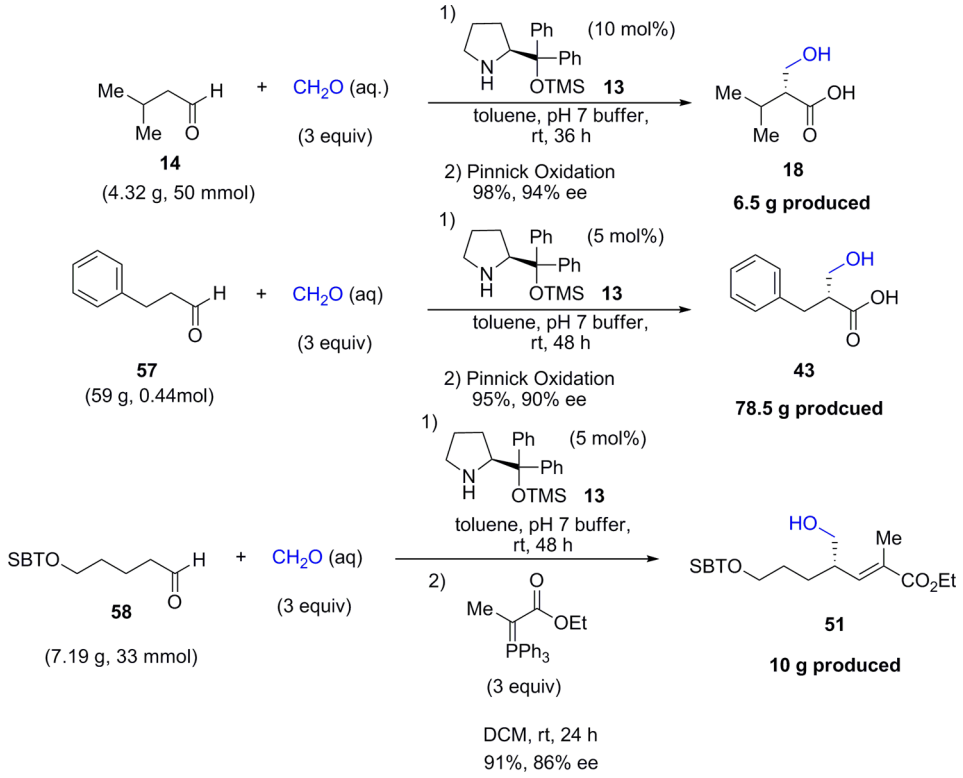
Figure 2. Known limitations on the scope of enantioselective α-hydroxymethylation.

may be a result of the formation of an unusually stable enamine upon reaction with aminocatalyst **13**. While this type of aldehyde has successfully been employed in other organocatalytic reactions, they typically require higher reaction temperatures and the presence of acid for efficient reaction to occur.[35] Under the optimized reaction conditions utilized above at elevated temperatures, our expectation would be that elimination and/or erosion of stereocontrol would occur. In the case of aldehydes **54**−**56**, the resulting enamines are notoriously unstable and decompose under the reaction conditions. In common with aldehydes of the structural framework of **53**, aldehydes **54**, **55**, and **56** have been employed in other organocatalytic reactions using different catalysts and usually under nonaqueous reaction conditions (Figure 2).[36]

Studies of the Scalability of the Enantioselective α-Hydroxymethylation Protocol. The scalability of the

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

Scheme 8. Scaled Examples of Enantioselective Hydroxymethylation



foregoing α-hydroxymethylation protocol was then examined. Gratifyingly, we have shown that the reaction is quite readily scalable affording the expected products in comparable yields and enantioselectivity with minimal modifications to the optimal experimental protocol. As shown in Scheme 8, the reactions affording hydroxy acids **18** and **43**, as well as unsaturated ester **51** have been conducted on 33−440 mmol scale in high yield and enantioselectivity. It should be noted that all of these reactions have proven highly reproducible on a number of different reaction scales.

In conclusion, we have developed a highly effective and general direct organocatalytic enantioselective α-hydroxymethylation of aldehydes. The procedure has been demonstrated to be effective in obtaining β-hydroxycarboxylic acids and -hydroxy-α,β-unsaturated esters in high yields and stereoselectivity. Future work will be directed to identifying additional applications of this methodology and further exploration of the chemistry of the intermediate lactol.

EXPERIMENTAL SECTION

General Information. All nonaqueous reactions were carried out using flame-dried glassware under an atmosphere of argon. All aqueous reactions were carried out using glassware that was not flame-dried and under an atmosphere of air capped with either a rubber septum or plastic septum (specified in the procedures below). All reactions were performed with magnetic stirring unless noted otherwise.

Chromatography. Liquid chromatography was performed on EMD silica gel 60 (230−400 mesh, particle size 0.040−0.063 mm) using the specified solvent system as eluent. For analytical purposes, thin-layer chromatography was performed using EMD silica 60 F254 precoated glass plates. Plates were analyzed by short wave UV illumination and/or through employment of a specific stain.

Potassium Permanganate Stain ($KMnO_4$). Prepared by dissolving potassium permanganate ($KMnO_4$) (3 g) and potassium carbonate (K_2CO_3) (20 g) in a 5% sodium hydroxide (NaOH) solution (5 mL) and deionized H_2O (300 mL) to give a purple solution.

***para*-Anisaldehyde Stain.** Prepared by the slow addition of concentrated sulfuric acid (20.5 mL) to a mixture of anh ethanol (530 mL) and H_2O (28 mL). The contents were then cooled to 0 °C and treated with glacial acetic acid (6.2 mL) and *p*-anisaldehyde (15.0 mL). The resulting solution should be a clear to pale yellow color.

Solvents and Reagents. All workup procedures involved reagent grade solvents. Reaction solvents were obtained from a solvent purification system except for the α-hydroxymethylation procedures where reagent grade solvents were used without drying. Deionized water was used anywhere that water is included in the procedure.

Commercially Available Reagents. Starting aldehydes were either purchased and used without purification or synthesized through the previous literature precedent indicated. All α,α-diarylprolinol catalysts were synthesized through known procedures with the indicated modifications discussed herein from commercially available L-proline. Formaldehyde (37% solution) was purchased from J.T. Baker Chemicals. The commercial pH 7 solid buffer consists of dibasic sodium phosphate and monobasic potassium phosphate. Sodium chlorite ($NaClO_2$) and sodium phosphate, monobasic, monohydrate ($NaH_2PO_4{\cdot}H_2O$) were purchased and used directly.

Preparation of Phosphate Buffer. Prepared by mixing potassium dibasic hydrogen phosphate (64.9 g, 0.477 mol, 1 equiv) and potassium monobasic hydrogen phosphate (91.1 g, 0.523 mol, 1.10 equiv) in a grinder and processing until a free-flowing uniform solid formed. (Note: This can also be performed using a mortar and pestle.)

Physical Data. ^{1}H NMR and ^{13}C NMR spectra were obtained on a 500 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane and are internally referenced to the deuterated solvent. ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constant (Hz), number of hydrogens). Multiplicities are denoted accordingly: s (singlet), b (broad signal), d (doublet), dd (doublet of coublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), dq (doublet of quartets), t (triplet), q (quartet), p (pentet), m (multiplet). Infrared spectra (IR) were acquired on an FT-IR (ATR) taken neat and are

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained employing ionization techniques consisting of electron impact (EI) or chemical ionization (CI) on a mass analyzer (MAT 95XL). Optical rotation values were measured on a polarimeter. Samples were inserted into a cell with a path length of 1 dm. Melting points were determined using a capillary melting point apparatus. Elemental analyses were obtained using an autobalance and determined by an analyzer. Enantiomeric excess was either determined by chiral GC by analysis of the racemic material using a CP-Chirasil-DEX CB column (25 m × 25 mm × 0.25 mm) utilizing a gas chromatograph (GC) with an integrator or by supercritical fluid chromatography (SFC) analysis with a SFC instrument equipped with a high-pressure diode array UV−vis detector, a back-pressure regulator, and a carbon dioxide pump, using a Diacel Chiralpak IA column or a Diacel Chiralpak IC column for enantiomer separation.

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol (12). A 1 L three-necked round-bottomed flask equipped with an egg-shaped Teflon coated magnetic stir bar, a Friedrich's condenser capped with a rubber septum in the middle neck, and 250 mL pressure equalizing addition funnel capped with a rubber septum in the right neck was charged with magnesium turnings (6.7 g, 275 mmol, 2.75 equiv) through the remaining open neck. The flask was sealed by capping the open neck with a rubber septum and stirring was initiated. The apparatus was then put under an atmosphere of argon and flame-dried. After allowing the apparatus to cool to ambient temperature, a crystal of iodine (50 mg, 0.2 mmol) was dissolved in 125 mL of anhydrous THF and added via syringe resulting in a light brown colored transparent solution. Bromobenzene (26.3 mL, 39.3 g, 250 mmol, 2.5 equiv) was then added to the addition funnel, and one-quarter of the volume was added to the flask. The flask was then heated by a 1 L electric mantle until the iodine color dissipated. Heating was stopped, and 125 mL of anhydrous THF was added to the addition funnel to dilute the bromobenzene. The bromobenzene solution was then added dropwise to the flask at a rate sufficient to maintain reflux in the flask (added over 20 min). The clear solution became cloudy and brown during the addition. When the addition was complete, heat was reapplied and the flask was allowed to stir at reflux for 1 h. Heating was discontinued, and the brown cloudy reaction mixture containing unused magnesium was cooled to room temperature. *N*-Boc-L-proline methyl ester (**10**)[37,38] (22.9 g, 100 mmol, 1 equiv) was then dissolved in anhydrous THF (200 mL), and added dropwise to the Grignard solution via the same addition funnel over 45 min. The reaction was stirred at ambient temperature for 1.5 h and subsequently cooled to 0 °C in an ice water bath. The reaction was quenched by controlled addition of a saturated aqueous solution of ammonium chloride (150 mL) via addition funnel over 5 min. The biphasic mixture was transferred to a 2 L separatory funnel and diluted with water (150 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried over sodium sulfate and gravity filtered through a large powder funnel equipped with a conical medium porosity filter paper into a 1 L single-necked (24/40) round-bottomed flask. The solvent was removed from the filtrate by rotary evaporation (30 mmHg) at room temperature providing a clear colorless residue. The flask containing the previously prepared residue was equipped with an egg-shaped Teflon-coated magnetic stir bar (15 × 32 mm). Ethanol (500 mL) was subsequently added to the flask, followed by sodium hydroxide (40 g, 1 mol, 10 equiv) and stirring was initiated. The flask was then fitted with a Friedrich's condenser open to the atmosphere and heated to reflux using a 1 L electric mantle and allowed to stir at reflux for 1 h. Heating was discontinued, the Friedrich's condenser removed, and the reaction was concentrated by rotary evaporation using a 50 °C water bath (30 mmHg) providing a light yellow amorphous solid. The residue was dissolved in water (200 mL) and diethyl ether (200 mL), and the resulting biphasic mixture was transferred to a 1 L separatory funnel. The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were washed with water (200 mL) and then a saturated aqueous solution of sodium chloride (200 mL). The organic layers were then concentrated by rotary evaporation (50 mmHg) at room temperature to afford a light yellow solid. The solid was dissolved in boiling hexanes (200 mL), decolorizing carbon (2.5 g) was added, and the solution was filtered hot through a large powder funnel equipped with a conical medium porosity filter paper into a 500 mL Erlenmeyer flask containing refluxing hexanes (30 mL). Once the filtration was complete, the flask was cooled to 0 °C and aged at 0 °C for 1 h resulting in crystallization. The hexanes were then decanted off and the white crystals were washed three times with 20 mL of cold (0 °C) hexanes washes (3 × 20 mL) and the washes successively decanted. The resulting crystal solid was transferred to a 250 mL 24/40 single-necked round-bottomed flask that was then fitted with a vacuum adaptor and dried on a vacuum pump (0.15 mmHg) overnight (14 h) to provide (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**12**) (15.9 g, 63%) as white crystals having mp = 74−77 °C. A second crop of crystals were obtained by concentrating the mother liquor and hexanes washes by rotary evaporation (30 mmHg) to dryness, dissolving the residue in boiling hexanes (50 mL), then cooling the solution to 0 °C and aging the solution for 1 h at 0 °C. After isolation by decantation, the resulting crystalline solids were washed three times with cold hexanes (10 mL) and isolated by decantation and dried under vacuum (0.15 mmHg) overnight (14 h) as above to give 3.0 g (12%) of white crystals of comparable purity to the first crop: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.57 (dd, J = 8.4, 1.1 Hz, 2H), 7.50 (dd, J = 8.4, 1.2 Hz, 2H), 7.31−7.26 (m, 5H), 7.18−7.14 (m, 2H), 4.59 (s, 1H), 4.26 (t, J = 7.7 Hz, 1H), 3.04 (ddd, J = 9.1, 6.6, 5.0 Hz, 1H), 2.97−2.93 (m, 1H), 1.78−1.54 (m, 6H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 148.3, 145.5, 128.3, 128.1, 126.57, 126.46, 126.0, 125.7, 64.6, 46.9, 26.4, 25.6; IR (ATR) (cm^{-1}) 3352, 3059, 3024, 2966, 2947, 2870, 1597, 1493, 1447, 1369, 1173, 991, 748, 698, 660, 636; MS (APCI+) m/z (relative intensity) 253.8 ([M + H$^+$], 100%), 285.8 ([M + H$^+$ + MeOH], 22%). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60, H, 7.56, N, 5.53. Found: C, 80.64, H, 7.68, N, 5.49.

(*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (13). A 1 L 24/40 single-necked round-bottomed flask was equipped with an egg-shaped Teflon-coated magnetic stir bar (15 × 32 mm) and a 60 mL pressure equalizing addition funnel fitted with a rubber septum. The flask was placed under an atmosphere of argon and flame-dried. After cooling to ambient temperature, a solution of (*S*)-diphenyl-(pyrrolidin-2-yl)methanol (**12**) (17.7 g, 70 mmol, 1 equiv) in anhydrous DCM (350 mL) was charged into the flask. The solution was cooled to −78 °C in a dry ice and acetone bath, followed by addition of triethylamine (12.7 mL, 9.2 g, 91 mmol, 1.3 equiv) in one portion. Trimethylsilyl trifluoromethanesulfonate (16.5 mL, 20.2 g, 91 mmol, 1.3 equiv) was added dropwise via the addition funnel over 30 min. The reaction mixture was then stirred and allowed to warm to 0 °C over 2 h. The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature over 1 h. The reaction was quenched by addition of a solution of sat aq sodium bicarbonate (100 mL) over 30 s. The mixture was diluted with water (100 mL) and transferred to a 1 L separatory funnel. The phases were separated, and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic phases were dried over anhydrous sodium sulfate and gravity filtered through a powder funnel equipped with medium porosity conical filter paper. The filtrate was concentrated by rotary evaporation (30 mmHg) to afford the crude product as an orange oil. Purification by column chromatography with elution by 60% diethyl ether/hexanes yielded (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-pyrrolidine (**13**) (18.3 g, 80%) as a light yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.46 (dd, J = 8.3, 1.1 Hz, 2H), 7.36−7.35 (m, 2H), 7.29−7.19 (m, 7H), 4.03 (t, J = 7.3 Hz, 1H), 2.88−2.77 (m, 2H), 1.64−1.52 (m, 5H), 1.40−1.35 (m, 1H), −0.09 (s, 9H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 128.5, 127.72, 127.68, 127.64, 127.01, 126.84, 83.3, 65.5, 47.3, 27.6, 25.2, 2.3; IR (ATR) (cm^{-1}) 3060, 3024, 2955, 2897, 2874, 1493, 1447, 1404, 1246, 1068, 879, 833, 752, 698; MS (APCI+) m/z (relative intensity) 325.9 ([M + H$^+$], 100%), 357.9 ([M + H$^+$ + MeOH], 4%). Anal. Calcd for $C_{20}H_{27}NOSi$: C, 73.79, H, 8.36, N, 4.30. Found: C, 73.74, H, 8.41, N, 4.21.

Procedure A: General Procedure for the α-Hydroxymethylation and Pinnick Oxidation of Aldehydes (Preparation of Racemic Material). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with pyrrolidine (0.017 mL, 0.20 mmol,

DOI: 10.1021/acs.joc.5b00380
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0.10 equiv), pH 7 buffer (1.0 g), and toluene (4 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). The resulting biphasic mixture was allowed to stir for 15 min before freshly distilled aldehyde (2.0 mmol, 1 equiv) was added and the vessel was capped with a yellow hard plastic Caplug. The reaction was then stirred for the indicated time period (Note: reaction monitored by ^{1}H NMR analysis of a direct aliquot of the toluene layer until absence of starting material was observed). The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The resulting oil was then redissolved in *t*-butanol (10 mL) and 2-methyl-2-butene (90%, 2.35 mL, 20 mmol, 10.0 equiv) and allowed to stir. To the stirring solution was added a solution of $NaClO_2$ (80%, 0.9 g, 8.0 mmol, 4.0 equiv) and $NaH_2PO_4{\cdot}H_2O$ (1.1 g, 8.0 mmol, 4.0 equiv) in H_2O (5 mL) (Note: When performing this step on large scale, this step should be performed by precooling the *t*-butanol/2-methyl-2-butene/substrate mixture to 0 °C, as it produces a slight exotherm) and the reaction was capped with a rubber septum with a needle as outlet. The resulting green biphasic solution was stirred for 6 h (Note: reaction progressively turns to a cloudy colorless solution) at which point the solvent was removed in vacuo to afford a watery residue. The residue was then diluted with EtOAc (10 mL), 10% HCl (2.5 mL), and brine (2.5 mL). The aqueous layer was then extracted with EtOAc (3 × 10 mL), the organic extracts were dried with Na_2SO_4, and the solvent was removed in vacuo to afford a clear oil. The resulting oil was then purified via flash chromatography to afford the target *β*-hydroxycarboxylic acid. (Note: this reaction suffers from a significant amount of *α*-methylenation, but generally provided enough material for preparation of racemic samples. In the situations where this is not the case, racemic 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (***rac*-13**) was employed as the organocatalyst).

Procedure B: General Procedure for the *α*-Hydroxymethylation and Pinnick Oxidation of Aldehydes (Preparation of Enantioenriched Material). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**13**) (0.195 g, 0.6 mmol, 0.30 equiv), pH 7 buffer (0.5 g), and toluene (4 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled aldehyde (2.0 mmol, 1 equiv) was added and the vessel was capped with a yellow hard plastic Caplug. The reaction was then stirred for the indicated time period (Note: reaction monitored by ^{1}H NMR analysis of a direct aliquot of the toluene layer until absence of starting material was observed). The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The toluene extracts were concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was then redissolved in *t*-butanol (10 mL) and 2-methyl-2-butene (90%, 2.35 mL, 20 mmol, 10.0 equiv) and allowed to stir. To the stirring solution was added a solution of $NaClO_2$ (80%, 0.9 g, 8.0 mmol, 4.0 equiv) and $NaH_2PO_4{\cdot}H_2O$ (1.1 g, 8.0 mmol, 4.0 equiv) in H_2O (5 mL) and the reaction was capped with a rubber septum with a needle as outlet (Note: When performing this step on large scale, precooling the *t*-butanol/2-methyl-2-butene/substrate mixture to 0 °C is required, as it produces a slight exotherm). The resulting green biphasic solution was stirred for 6 h (Note: reaction progressively turns to a cloudy colorless solution) at which point the solvent was removed in vacuo to afford a watery residue. The residue was then diluted with EtOAc (10 mL), 10% HCl (2.5 mL), and brine (2.5 mL). The aqueous layer was then extracted with EtOAc (3 × 10 mL), the organic extracts were dried with Na_2SO_4, and the solvent was removed in vacuo to afford a clear oil. The resulting oil was purified via flash chromatography to afford target *β*-hydroxycarboxylic acid (Note: Any procedures that deviate from the stated procedure have been indicated below).

General Procedure for Methyl Esterification of *β*-Hydroxyacids. A 10 mL round-bottom flask equipped with magnetic stir bar was charged with starting *β*-hydroxyacid (0.4 mmol) and *N*,*N*-dimethylformamide (1 mL). The mixture was treated with potassium carbonate (0.11 g, 0.8 mmol, 2 equiv) and iodomethane (0.027 mL, 0.44 mmol, 1.1 equiv) and the reaction was stirred for 15 h at room temperature, progressively turning cloudy. The reaction mixture was quenched with water (1 mL) and diluted with diethyl ether (2 mL) and stirred until all suspended solids were dissolved. The organic layer was removed and additional extractions were performed with Et_2O (2 × 2 mL). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated in vacuo to afford the crude methyl ester that was used directly for analysis of enantioselectivity.

General Procedure for Benzyl Esterification of *β*-Hydroxyacids. A 10 mL round-bottom flask equipped with magnetic stir bar was charged with starting *β*-hydroxyacid (0.4 mmol) and *N*,*N*-dimethylformamide (1 mL). The mixture was treated with potassium carbonate (0.11 g, 0.8 mmol, 2 equiv) and benzyl bromide (0.052 mL, 0.44 mmol, 1.1 equiv) and the reaction was stirred for 15 h at room temperature, progressively turning cloudy. The reaction mixture was quenched with water (1 mL) and diluted with diethyl ether (2 mL) and stirred until all suspended solids were dissolved. The combined organic layer was removed and additional extractions were performed with Et_2O (2 × 2 mL). The organic extracts were dried with anhydrous sodium sulfate and concentrated in vacuo to afford the crude benzyl ester that was used directly for analysis of enantioselectivity.

Procedure C: General Procedure for the *α*-Hydroxymethylation and Wittig Olefination of Aldehydes (Preparation of Racemic Material). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with pyrrolidine (0.017 mL, 0.2 mmol, 0.10 equiv), pH 7 buffer (1.0 g), and toluene (4 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled aldehyde (2.0 mmol, 1 equiv) was added and the vessel was capped with a yellow hard plastic Caplug. The reaction was then stirred for the indicated time period (Note: reaction monitored by ^{1}H NMR analysis of a direct aliquot of the toluene layer until absence of starting material was observed). The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was redissolved in DCM (2 mL) and subsequently added to a solution of ethyl 2-(triphenylphosphoranylidene)propanoate (2.17 g, 6.0 mmol, 3.0 equiv) in dichloromethane (6 mL) dropwise via glass pipet at room temperature and the vessel was capped with a rubber septum (Note: On large scale this addition can be done via a pressure equalizing addition funnel). The resulting green mixture was stirred for 24 h at room temperature. Upon completion by TLC analysis, the reaction mixture was poured through a plug of Celite and concentrated in vacuo to afford a green residue. The resulting residue was purified via flash chromatography to afford the target esters (Note: this reaction suffers from a significant amount of *α*-methylenation, but generally provided enough material for preparation of a racemate samples. In samples when this is not the case, racemic 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (***rac*-13**) was employed as the organocatalyst).

Procedure D: General Procedure for the *α*-Hydroxymethylation and Wittig Olefination of Aldehydes (Preparation of Enantioenriched Material). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**13**) (0.195 g, 0.6 mmol, 0.30 equiv), pH 7 buffer (1.0 g), and toluene (4 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled aldehyde (2.0 mmol, 1.0 equiv) was added and the vessel was capped with a yellow hard plastic Caplug. The reaction was then stirred for the indicated time period (Note: reaction monitored by ^{1}H NMR analysis of a direct aliquot of the toluene layer until absence of starting material was observed). The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The combined toluene

DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045

extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was then redissolved in DCM (2 mL) and subsequently added to a solution of ethyl 2-(triphenylphosphoranylidene)propanoate (2.17 g, 6.0 mmol, 3.0 equiv) in DCM (6 mL) dropwise via glass pipet at room temperature and the vessel was capped with a rubber septum (Note: On large scale this addition can be done via a pressure equalizing addition funnel). The resulting green mixture was stirred 24 h at room temperature. Upon completion by TLC analysis, the reaction mixture was poured through a plug of Celite and concentrated in vacuo to afford a green residue. The resulting residue was purified via flash chromatography to afford the target esters (Note: Any procedures that deviate from the stated procedure have been indicated below).

5-Isopropyl-1,3-dioxan-4-ol (*rac*-15). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with racemic 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (***rac*-13**) (0.195 g, 0.6 mmol, 0.30 equiv), pH 7 buffer (0.5 g), and toluene (4 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled isovaleraldehyde (0.172 g, 0.21 mL, 2.0 mmol, 1.0 equiv) was added and the vessel was capped with a yellow hard plastic caplug. The reaction was then stirred for the 15 h at room temperature at which point ^{1}H NMR analysis of a direct aliquot of the toluene layer of the reaction mixture showed full consumption of starting material. The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The combined toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature) to afford a clear oil. The resulting oil was subsequently purified via flash chromatography (30% diethyl ether/hexanes) to afford target lactol as a clear oil (0.076 g, 26%): ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.83 (t, J = 0.8 Hz, 1H), 5.34 (d, J = 2.7 Hz, 2H), 5.21 (d, J = 5.9 Hz, 2H), 5.12 (d, J = 6.2 Hz, 2H), 4.94 (d, J = 6.2 Hz, 2H), 4.77 (s, 1H), 4.72−4.68 (m, 3H), 4.07 (dd, J = 11.5, 4.1 Hz, 1H), 3.96−3.93 (m, 3H), 3.76 (q, J = 10.5 Hz, 3H), 3.62 (dd, J = 11.6, 8.3 Hz, 1H), 3.40 (s), 2.78 (s, 1H), 2.48 (s, 2H), 2.40 (s, 1H), 2.30 (s), 2.20−2.12 (m, 2H), 2.00 (dt, J = 12.8, 6.6 Hz, 1H), 1.80−1.74 (m, 2H), 1.59 (t, J = 18.4 Hz, 3H), 1.48−1.43 (m, 2H), 1.27 (s, 1H), 1.06−0.86 (m, 31H); ^{13}C NMR (126 MHz; CDCl3) δ 96.1, 91.9, 89.8, 85.5, 66.0, 65.7, 46.9, 45.7, 31.7, 26.25, 26.09, 22.8, 20.9, 20.16, 19.99, 19.2, 14.3.

Note 1: Decomposition of this compound was observed both neat and in solution in a variety of solvents over the course of 5 h, not allowing for full characterization.

Note 2: The ^{1}H and ^{13}C NMR contains a mixture of diastereomers and oligomers and is incorporated into the Supporting Information only for reference.

(*R*)-2-((((*tert*-Butyldimethylsilyl)oxy)methoxy)methyl)-3-methylbutanal and *tert*-butyl(((5*R*)-5-Isopropyl-1,3-dioxan-4-yl)oxy)dimethylsilane (16 and 17). To a stirred solution of (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**13**) (0.39 g, 1.2 mmol, 0.30 equiv) in toluene (8.0 mL) was added solid pH 7 buffer (0.20 g) followed by aqueous formaldehyde solution (37% aq, 1.0 mL, 12.0 mmol, 3.0 equiv) at rt. To the vigorously stirred suspension was added aldehyde (0.43 mL, 0.34 g, 4.0 mmol) in one portion and the resulting suspension was stirred for 12 h. The two layers were then separated and the toluene concentrated in vacuo (Caution: keep the water bath temperature <40 °C while evaporating). The residue was then redissolved in DCM (5.0 mL) and added to a premixed solution of imidazole (0.35 g, 5.2 mmol, 1.3 equiv) and TBSCl (0.60 g, 5.2 mmol, 1.3 equiv) stirred for 20 min at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 7 h at 0 °C before being concentrated in vacuo. Purification of this material via column chromatography on silica gel (with elution by 100% hexanes−2% ethyl acetate/hexanes) provided an inseperable 3:1 mixture of aldehyde **16** and lactol **17** as a clear oil (0.55 g, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (d, J = 3 Hz, 1H), 4.83 (s, 2H), 3.95−3.75 (m, 2H), 2.40 (m, 1H), 2.15 (m, 1H), 1.04 (dd, J_1 = 7 Hz, J_2 = 5 Hz, 6H), 0.95 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 93.0, 64.8, 58.0, 26.0, 25.7, 20.4, 19.9, −5.0; IR (neat) 2959, 2858, 1724, 1253, 1041, 833, 780 cm^{-1}; HRMS Calcd for $C_9H_{19}O_3Si$ (M^+ − ^{t}Bu) 203.1098, found 203.1094 (EI); $[\alpha]_{D20}$ −10.5° (c 2.0, DCM).

Note: Although the above mixture of compounds was purified via flash chromatography, resolution of enantiomers of the mixture proved difficult. As a result, we find that the crude reaction product above is pure enough for further elaboration. The ^{1}H NMR and ^{13}C NMR spectra for the crude material are provided in the Supporting Information as well as spectra of the above mixture with arrows indicating which shifts correspond to the respective products.

(*R*)-2-(Hydroxymethyl)-3-methylbutanoic acid (18). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from isovaleraldehyde (α-hydroxymethylation reaction time was 15 h). The resulting crude clear oil was then purified via flash chromatography (gradient: DCM → 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)-3-methylbutanoic acid as a white solid (0.248 g, 94%, 94% ee) having mp 76−80 °C: R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.91 (s, 2H), 3.89−3.85 (m, 1H), 3.81−3.78 (m, 1H), 2.44−2.41 (m, 1H), 2.06−2.01 (m, 1H), 0.99 (t, J = 5.9 Hz, 6H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 180.3, 61.5, 54.3, 27.8, 20.7, 20.2; IR (neat) 3263, 2962, 2877, 2631, 1704, 1196, 1010 cm^{-1}; HRMS Calcd for $C_6H_{13}O_3$ (M^+ + H) 133.0859, found 133.0862 (CI); $[\alpha]_{D20}$ −6,2° (c 4.8, $CHCl_3$). GC Analysis: T_{inj} = 250 °C, T_{det} = 275 °C, flow = 2 mL/min, t_i = 70 °C (1 min), t_f = 160 °C, rate = 3 °C/min, retention times of methyl ester: t_{maj} = 15.656, t_{min} = 15.397.

(*R*)-2-(Hydroxymethyl)pentanoic acid (38). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from valeraldehyde (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (DCM → 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)pentanoic acid as a clear oil (0.248 g, 94%, 93% ee): R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.47 (s, 2H), 3.76 (sextet, J = 6.1 Hz, 2H), 2.61 (quintet, J = 6.1 Hz, 1H), 1.63 (dq, J = 14.1, 7.3 Hz, 1H), 1.48 (dq, J = 14.3, 7.1 Hz, 1H), 1.38 (sextet, J = 7.5 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (500 MHz; $CDCl_3$) δ 180.6, 63.1, 47.4, 30.5, 20.5, 14.1; IR (neat) 3367, 2959, 2935, 2874, 2661, 1709, 1466, 1196, 1053 cm^{-1}; HRMS Calcd for $C_6H_{13}O_3$ (M^+ + H) 133.0859, found 133.0856 (CI); $[\alpha]_{D20}$ −4.2° (c 10, $CHCl_3$). GC Analysis: T_{inj} = 250 °C, T_{det} = 275 °C, flow = 2 mL/min, t_i = 70 °C (1 min), t_f = 200 °C, rate = 1 °C/min, retention times of methyl ester: t_{maj} = 29.905, t_{min} = 29.585.

(*R*)-2-(Hydroxymethyl)-3,3-dimethylbutanoic acid (39). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from 3,3-dimethylbutyraldehyde (α-hydroxymethylation reaction time was 120 h). The resulting oil was then purified via flash chromatography (1% methanol/DCM→ 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)-3,3-dimethylbutanoic acid as a white solid (0.202 g, 69%, 90% ee) having mp 129−133 °C: R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 5.06 (s, 2H), 3.97 (t, J = 10.5 Hz, 1H), 3.83 (dd, J = 10.8, 3.9 Hz, 1H), 2.51 (dd, J = 10.2, 3.9 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (126 MHz; CDCl3) δ 179.3, 61.3, 58.3, 32.2, 28.5; IR (neat) 3379, 3290, 2692, 2878, 1701, 1659, 1339, 1041 cm^{-1}; HRMS Calcd for $C_7H_{15}O_3$ (M^+ + H) 147.1016, found 147.1019 (CI); $[\alpha]_{D20}$ −13.3° (c 2.9, $CHCl_3$). GC Analysis: T_{inj} = 250 °C, T_{det} = 275 °C, flow = 2 mL/min, t_i = 40 °C (1 min), t_f = 200 °C, rate = 4 °C/min, retention times of methyl ester: t_{maj} = 28.460, t_{min} = 28.033.

2-(Hydroxymethyl)-2-methylbutanoic acid (40). A 10 mL round-bottom flask equipped with magnetic stir bar and reflux condenser was charged with pyrrolidine (0.05 mL, 0.60 mmol, 0.30 equiv), pH 7 buffer (0.5 g), and toluene (2 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq., 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled 2-methylbutyraldehyde (0.172 g, 0.21 mL 2.0 mmol, 1 equiv) was added and the vessel was heated to reflux with attached condenser. The reaction was then stirred for 24 h at reflux. Heating was stopped, the reaction was allowed to cool to ambient temperature, and the toluene layer was then separated and an additional extraction with

DOI: 10.1021/acs.joc.5b00380
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toluene (1 mL) was performed. The toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was then redissolved in *t*-butanol (10 mL) and 2-methyl-2-butene (90%, 2.35 mL, 20 mmol, 10.0 equiv) and allowed to stir via magnetic stirring for 6 h. To the stirring solution was added a solution of $NaClO_2$ (80%, 0.9 g, 8.0 mmol, 4.0 equiv) and $NaH_2PO_4{\cdot}H_2O$ (1.1 g, 8.0 mmol, 4.0 equiv) in H_2O (5 mL) and the reaction was capped with a rubber septum with a needle as outlet. The resulting green biphasic solution was stirred for 6 h (Note: reaction progressively turns to a cloudy colorless solution) at which point the solvent was removed in vacuo to afford a watery residue. The residue was then diluted with EtOAc (10 mL), 10% HCl (2.5 mL), and brine (2.5 mL). The aqueous layer was then extracted with EtOAc (3 × 10 mL), the organics were dried with Na_2SO_4, and the solvent was removed in vacuo to afford a clear oil. The resulting oil was then purified via flash chromatography (DCM→ 5% methanol/DCM) to afford 2-(hydroxymethyl)-2-methylbutanoic acid (0.206 g, 78%) as a white solid having mp =51−54 °C. (Note: This reaction was attempted with (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-pyrrolidine (**13**), but still furnished racemic product. SFC chromatograms are provided in the Supporting Information for both of these runs: R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.11 (s, 2H), 3.75 (d, J = 11.3 Hz, 1H), 3.53 (d, J = 11.3 Hz, 1H), 1.72−1.56 (m, 2H), 1.19 (s, 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 183.0, 67.8, 48.1, 28.5, 18.9, 8.7; IR (neat) 3302, 2970, 2882, 1701, 1462, 1258, 1045 cm^{-1}; HRMS Calcd for $C_6H_{13}O_3$ (M^+ + H) 133.0859, found 133.0855. SFC Analysis: Diacel Chiralpak IA (0.46 cm ID × 25 cm L), 5% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 5.20, 5.49.

(*R*)-2-(Hydroxymethyl)-2,3-dimethylbutanoic acid (41). A 10 mL round-bottom flask equipped with magnetic stir bar and reflux condenser was charged with (*S*)-2-(diphenyl((trimethylsilyl)oxy)-methyl)pyrrolidine (**13**) (0.195 g, 0.6 mmol, 0.30 equiv), pH 7 buffer (1.0 g), and toluene (2 mL) and stirring was initiated. To the vigorously stirring solution was added aqueous formaldehyde solution (37% aq, 0.5 mL, 6.0 mmol, 3.0 equiv). This was allowed to stir for 15 min before freshly distilled 2,3-dimethylbutyraldehyde[39] (0.200 g, 2.0 mmol, 1 equiv) was added and the vessel was heated to reflux with attached condenser. The reaction was stirred for 68 h at reflux. Heating was stopped, the reaction was allowed to cool to ambient temperature, and the toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was then redissolved in *t*-butanol (10 mL) and 2-methyl-2-butene (90%, 2.35 mL, 20 mmol, 10.0 equiv) and allowed to stir via magnetic stirring for 6 h. To the stirring solution was added a solution of $NaClO_2$ (80%, 0.9 g, 8.0 mmol, 4.0 equiv) and $NaH_2PO_4{\cdot}H_2O$ (1.1 g, 8.0 mmol, 4.0 equiv) in H_2O (5 mL) and the reaction was capped with a rubber septum with a needle as outlet. The resulting green biphasic solution was stirred for 6 h (Note: reaction progressively turns to a cloudy colorless solution) at which point the solvent was removed in vacuo to afford a watery residue. The residue was then diluted with EtOAc (10 mL), 10% HCl (2.5 mL), and brine (2.5 mL). The aqueous layer was then extracted with EtOAc (3 × 10 mL), the organic extracts were dried with Na_2SO_4, and the solvent was removed in vacuo to afford a clear oil. The resulting oil was then purified via flash chromatography (1% methanol/DCM→ 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)-2,3-dimethylbutanoic acid (0.105 g, 36%, 19% ee) as a white solid having mp = 50−54 °C: R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.81 (d, J = 11.2 Hz, 1H), 3.55 (d, J = 11.3 Hz, 1H), 2.13 (dt, J = 13.7, 6.9 Hz, 1H), 1.13 (s, 3H), 0.94 (dd, J = 6.9, 2.6 Hz, 6H); ^{13}C NMR (126 MHz; CDCl3) δ 182.98, 66.9, 51.2, 31.8, 17.9, 17.4, 15.0; IR (neat) 3283, 2963, 2877, 1701, 1555, 1466, 1254, 1030 cm^{-1}. Anal. calcd for $C_7H_{14}O_3$: C, 57.51, H, 9.65. Found: C, 57.60, H, 9.58; $[\alpha]_{D20}$ −7.2° (*c* 1.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 5% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 5.49 (40.67%), 5.73 (59.33%).

(*R*)-2-(Hydroxymethyl)hept-6-ynoic acid (42). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from hept-6-ynal[40] (α-hydroxymethylation reaction time was 12 h). The resulting oil was then purified via flash chromatography (1% methanol/DCM→ 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)hept-6-ynoic acid as a yellow oil (0.211 g, 68%, 91% ee): R_f = 0.2 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.82 (d, J = 5.7 Hz, 2H), 2.65 (quintet, J = 6.3 Hz, 1H), 2.24 (td, J = 6.6, 2.1 Hz, 2H), 1.97 (t, J = 2.2 Hz, 1H), 1.82 (dq, J = 14.4, 7.1 Hz, 1H), 1.75−1.61 (m, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 180.2, 83.8, 69.1, 63.1, 47.2, 27.4, 26.1, 18.5; IR (neat) 3291, 3163, 2943, 2631, 1709, 1196, 1026 cm^{-1}; HRMS Calcd for $C_8H_{13}O_3$ (M^+ + H) 157.0859, found 157.0861 (CI); $[\alpha]_{D20}$ −1.3° (*c* 2.9, $CHCl_3$). SFC Analysis: Diacel Chiralpak IA (0.46 cm ID × 25 cm L), 5% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 8.08 (95.70%), 9.31 (4.31%).

(*R*)-2-Benzyl-3-hydroxypropanoic acid (43). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from hydrocinnamaldehyde (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (DCM→ 5% methanol/DCM) to afford (*R*)-2-benzyl-3-hydroxypropanoic acid as a white solid (0.342 g, 95%, 92% ee) having mp = 60−64 °C: R_f = 0.3 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.65 (s, 1H), 3.83 (dd, J = 11.2, 2.8 Hz, 1H), 3.76 (dd, J = 11.2, 6.2 Hz, 1H), 3.11 (q, J = 9.2 Hz, 1H), 2.92−2.88 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 179.8, 138.3, 129.1, 128.8, 126.8, 62.0, 49.0, 34.2; IR (neat) 3283, 2947, 1705, 1196, 1030 cm^{-1}; HRMS Calcd for $C_{10}H_{12}O_3$ (M^+ + H) 180.0781, found 180.0788 (CI); $[\alpha]_{D20}$ +12.8° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IA (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of methyl ester: 2.20 (4.22%), 2.37 (95.78%).

(*R*)-2-(Hydroxymethyl)-6-methoxy-6-oxohexanoic acid (44). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from methyl-6-hexanoate[41] (α-hydroxymethylation reaction time was 20 h). The resulting oil was then purified via flash chromatography (DCM→ 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)-6-methoxy-6-oxohexanoic acid as a clear oil (0.346 g, 91%, 88% ee): R_f = 0.4 (5% methanol/DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (b, 2H), 3.68−3.64 (m, 2H), 3.62 (s, 3H), 2.50−2.47 (m, 1H), 2.31−2.29 (m, 2H), 1.63−1.56 (m, 3H), 1.45−1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 174.3, 62.9, 51.6, 48.1, 33.7, 27.8, 22.5; IR (neat) 3417, 2951, 2503, 1720, 1570, 1438, 1198, 1033, 910, 729 cm^{-1}; HRMS Calcd for $C_8H_{15}O_5$ (M^+ + H) 191.0914, found 191.0922 (CI); $[\alpha]_{D20}$ +11.2° (*c* 4.0, methanol). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 6.28 (94.24%), 6.71 (5.76%).

(*R*)-2-(Hydroxymethyl)-6-oxoheptanoic acid (45). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from 6-oxoheptanal[42] (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (DCM → 5% methanol/DCM) to afford (*R*)-2-(hydroxymethyl)-6-oxoheptanoic acid as a faint yellow oil (0.303 g, 87%, 96% ee): R_f = 0.4 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.66 (s, 2H), 3.79 (d, J = 5.8 Hz, 2H), 2.60 (quintet, J = 6.0 Hz, 1H), 2.48 (t, J = 6.7 Hz, 2H), 2.14 (s, 3H), 1.68−1.51 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 209.3, 179.5, 62.9, 47.3, 43.4, 30.1, 27.6, 21.3; IR (neat) 3287, 2947, 1701, 1362, 1180, 1045 cm^{-1}; HRMS Calcd for $C_8H_{15}O_4$ (M^+ + H) 175.0965, found 175.0965 (CI); $[\alpha]_{D20}$ +12.8° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 5.96 (97.93%), 10.44 (2.07%).

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-(hydroxymethyl)-pentanoic acid (46). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from 5-((*tert*-butyldimethylsilyl)oxy)-pentanal[43] (α-hydroxymethylation reaction time was 15 h). The

DOI: 10.1021/acs.joc.5b00380
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resulting oil was then purified via flash chromatography (DCM→ 5% methanol/DCM) to afford (*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pentanoic acid as a clear oil (0.493 g, 94%, 93% ee): R_f = 0.4 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.59 (s, 2H), 3.80−3.78 (m, 2H), 3.65 (dd, J = 5.6, 3.1 Hz, 2H), 2.64 (quintet, J = 5.5 Hz, 1H), 1.76−1.61 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 180.0, 63.10, 63.03, 47.2, 30.1, 26.1, 24.9, 18.5, −5.2; IR (neat) 3279, 2951, 2928, 2885, 1709, 1388, 1254, 1096, 833, 775 cm^{-1}; HRMS Calcd for $C_{12}H_{27}O_4Si$ (M^+ + H) 263.1673, found 263.1676 (CI); $[\alpha]_{D20}$ −6.8° (*c* 1.2, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester and TBS removed diol: 13.77 (96.51%), 22.59 (3.49%).

(Note: The TBS moiety is removed by dissolving the crude reaction mixture from benzyl protection in DCM (1 mL) and treating with 10% HCl (0.5 mL), stirring for 20 min, removing the DCM layer and using it directly for SFC analysis.)

(*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-(hydroxymethyl)-propanoic acid (47). The reaction was performed following the general procedure for α-hydroxymethylation and Pinnick oxidation (**Procedure B**) starting from *tert*-butyl(3-oxopropyl)carbamate[44] (α-hydroxymethylation reaction time was 30 h). The resulting oil was then purified via flash chromatography (DCM→ 10% methanol/DCM) to afford (*R*)-3-((*tert*-butoxycarbonyl)amino)-2-(hydroxymethyl)propanoic acid as a yellow oil (0.285 g, 65%, 91% ee): R_f = 0.1 (5% methanol/DCM); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.47 (s, 2H), 5.23 (s, 1H), 3.84 (s, 2H), 3.55−3.43 (m, 2H), 2.74 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 177.1, 157.6, 80.5, 59.8, 47.8, 37.9, 28.4; IR (neat) 3340, 2978, 1686, 1520, 1366, 1250, 1165, 1076, 1034 cm^{-1}; HRMS Calcd for $C_9H_{17}NO_5Na$ (M^+ + Na) 242.0999, found 242.0996 (CI); $[\alpha]_{D20}$ −7.5° (*c* 2.4, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min] of benzyl ester: 2.33 (95.42%), 2.96 (4.58%).

Ethyl (*S*,*E*)-4-(hydroxymethyl)-2-methylhept-2-enoate (48). The reaction was performed following the general procedure for α-hydroxymethylation and Wittig olefination (**Procedure D**) starting from valeraldehyde (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (50% hexanes/diethyl ether) to afford ethyl (*S*,*E*)-4-(hydroxymethyl)-2-methylhept-2-enoate as a clear oil (0.352 g, 88%, 90% ee): R_f = 0.5 (50% hexanes/diethyl ether); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.52 (dd, J = 10.4, 1.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.62 (dd, J = 10.6, 5.5 Hz, 1H), 3.51 (dd, J = 10.6, 7.7 Hz, 1H), 2.69−2.66 (m, 1H), 1.89 (d, J = 1.4 Hz, 3H), 1.51−1.47 (m, 2H), 1.33−1.25 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 168.2, 143.4, 130.3, 66.1, 60.8, 41.9, 33.4, 20.5, 14.42, 14.30, 13.2; IR (neat) 3449, 2955, 2932, 2870, 1708, 1269, 1219, 1126, 1096, 1038, 752 cm^{-1}. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97, H, 10.07. Found: C, 65.727, H, 10.128. $[\alpha]_{D20}$ +8.3° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 5% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min]: 5.59 (94.90%), 7.68 (5.10%).

Ethyl (*S*,*E*)-4-(hydroxymethyl)-2,5-dimethylhex-2-enoate (49). The reaction was performed following the general procedure for α-hydroxymethylation and Wittig olefination (**Procedure D**) starting from isovaleraldehyde (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (50% hexanes/diethyl ether) to afford ethyl (*S*,*E*)-4-(hydroxymethyl)-2,5-dimethylhex-2-enoate as a clear oil (0.348 g, 87%, 90% ee): R_f = 0.5 (50% hexanes/diethyl ether); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.62 (dd, J = 10.8, 1.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.75 (dd, J = 10.7, 5.0 Hz, 1H), 3.57 (dd, J = 10.7, 8.1 Hz, 1H), 2.47 (dtd, J = 11.2, 7.3, 4.3 Hz, 1H), 1.89 (d, J = 1.4 Hz, 3H), 1.79 (dq, J = 13.6, 6.8 Hz, 1H), 1.39 (s, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 168.1, 141.9, 131.0, 77.4, 77.2, 76.9, 64.4, 60.8, 48.2, 29.4, 20.9, 19.7, 14.4, 13.3; IR (neat) 3449, 2959, 2874, 1709, 1647, 1466, 1366, 1277, 1242, 1134, 1096, 1042, 748 cm^{-1}. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97, H, 10.07, O, 23.97. Found: C, 65.61, H, 10.16. $[\alpha]_{D20}$ +9.5° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 5% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min]: 4.89 (95.10%), 6.59 (4.9%).

Ethyl (*S*,*E*)-4-benzyl-5-hydroxy-2-methylpent-2-enoate (50). The reaction was performed following the general procedure for α-hydroxymethylation and Wittig olefination (**Procedure D**) starting from hydrocinnamaldehyde (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (50% hexanes/diethyl ether) to afford ethyl (*S*,*E*)-4-benzyl-5-hydroxy-2-methylpent-2-enoate as a clear oil (0.442 g, 89%, 84% ee): R_f = 0.5 (50% hexanes/diethyl ether); ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.36−7.34 (m, 3H), 7.28 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.4 Hz, 2H), 6.72 (dd, J = 10.1, 1.3 Hz, 1H), 4.30−4.24 (m, 2H), 3.76 (dt, J = 9.8, 4.6 Hz, 1H), 3.67 (t, J = 8.5 Hz, 1H), 3.05−2.97 (m, 1H), 2.92 (dd, J = 13.5, 6.3 Hz, 1H), 2.70 (dd, J = 13.5, 7.9 Hz, 1H), 1.76 (s, 3H), 1.53 (s, 1H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 168.0, 141.9, 139.3, 130.5, 129.2, 128.5, 126.4, 65.4, 60.8, 43.9, 37.5, 14.4, 12.9; IR (neat) 3437, 2932, 1705, 1451, 1273, 1219, 1103, 1030, 745, 698 cm^{-1}. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55, H, 8.12. Found: C, 72.478, H, 8.120. $[\alpha]_{D20}$ +23.2° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min]: 3.89 (92.08%), 5.35 (7.92%).

Ethyl (*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-(hydroxymethyl)-2-methylhept-2-enoate (51). The reaction was performed following the general procedure for α-hydroxymethylation and Wittig olefination (**Procedure D**) starting from 5-((*tert*-butyldimethylsilyl)-oxy)pentanal[43] (α-hydroxymethylation reaction time was 15 h). The resulting oil was then purified via flash chromatography (60% hexanes/diethyl ether) to afford ethyl (*S*,*E*)-4-benzyl-5-hydroxy-2-methylpent-2-enoate as a clear oil (0.621 g, 94%, 86% ee): R_f = 0.6 (50% hexanes/diethyl ether); ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.53 (dd, J = 10.3, 1.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.63 (dd, J = 10.7, 5.5 Hz, 1H), 3.58 (t, J = 6.2 Hz, 2H), 3.53 (t, J = 9.1 Hz, 1H), 2.70−2.63 (m, 1H), 1.88 (d, J = 1.4 Hz, 3H), 1.62−1.45 (m, 4H), 1.29 (t, J = 7.1 Hz, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz; CDCl3) δ 168.1, 143.1, 130.37, 130.36, 77.4, 66.0, 63.1, 60.8, 41.8, 30.4, 27.5, 26.1, 18.5, 14.4, 13.2, −5.2; IR (neat) 3453, 2932, 2859, 1709, 1254, 1211, 1096, 1049, 833, 775, 748 cm^{-1}. Anal. calcd for $C_{17}H_{34}O_4Si$: C, 61.77, H, 10.37. Found: C, 61.58, H, 10.46. $[\alpha]_{D20}$ +10.8° (*c* 2.0, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 10% *i*-PrOH in $scCO_2$, ν = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min]: 2.13 (92.95%), 2.71 (7.05%).

Ethyl (*S*,*E*)-5-hydroxy-2-methyl-4-(pyridin-3-ylmethyl)pent-2-enoate (52). A 10 mL round-bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-pyrrolidine (**13**) (0.195 g, 0.6 mmol, 0.30 equiv), pH 7 buffer (0.50 g), and toluene (4 mL) and stirring was initiated. To the stirring solution was added aqueous formaldehyde solution (37% aq., 0.5 mL, 6.0 mmol, 3.0 equiv) followed by freshly purified 3-(pyridin-3-yl)-propanal[45] (0.270 g, 2.0 mmol, 1 equiv) and capped with plastic septum and the resulting solution was stirred for 48 h, at which point ^{1}H NMR showed full consumption of starting material. The toluene layer was then separated and an additional extraction with toluene (1 mL) was performed. The combined toluene extracts were then concentrated in vacuo (Note: the water bath during concentration should remain at room temperature). The residue was then redissolved in DCM (2 mL) and added to a solution of ethyl 2-(triphenylphosphoranylidene)propanoate (2.17 g, 6.0 mmol, 3.0 equiv) in DCM (6 mL) dropwise via glass pipet at room temperature and the vessel was capped with a rubber septum. The resulting green mixture was stirred for 24 h at room temperature. Imidazole (0.177 g, 2.6 mmol, 1.3 equiv) and TBSCl (0.392 g, 2.6 mmol, 1.3 equiv) were added sequentially and the reaction mixture was let stir 30 min. The reaction mixture was poured through a plug of Celite and concentrated in vacuo to afford a green residue. The resulting residue was purified via flash chromatography (hexanes to 50% hexanes/Et_2O) to afford target compound as a clear oil (0.190 g, 52%, 83% ee): R_f = 0.5 (diethyl ether) ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.45−8.42 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.18 (dd, J = 7.7, 4.9 Hz, 1H), 6.61 (dd, J = 10.2, 1.3 Hz, 1H), 4.19−4.14 (m, 2H), 3.57 (dd, J = 5.5, 4.0 Hz, 2H),

DOI: 10.1021/acs.joc.5b00380
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2.98 (dd, J = 13.6, 5.6 Hz, 1H), 2.83−2.78 (m, 1H), 2.55 (dd, J = 13.6, 8.4 Hz, 1H), 1.62 (d, J = 1.3 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.05 (d, J = 2.6 Hz, 6H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 167.8, 150.6, 147.7, 141.3, 136.6, 135.1, 129.6, 123.2, 64.7, 60.6, 43.6, 34.4, 25.9, 18.4, 14.3, 12.7, −5.28, −5.39; IR (neat) 2951, 2928, 2855, 1709, 1470, 1254, 1231, 1099, 833, 775 cm^{-1}. Anal. calcd for $C_{20}H_{33}NO_3Si$: C, 66.07, H, 9.15, N, 3.85. Found: C, 65.99, H, 9.22, N, 4.074. $[\alpha]_D^{20}$ +30.1° (c 2.2, $CHCl_3$). SFC Analysis: Diacel Chiralpak IC (0.46 cm ID × 25 cm L), 3% i-PrOH in $scCO_2$, v = 4 mL/min, λ = 220 nm, 35 °C, 12 MPa; t_R [min]: 29.28 (8.52%), 32.59 (91.48%).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR spectra and GC, and SFC traces for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for partial support of these studies by Novartis Pharma AG and Novartis Pharmaceuticals Corp and the University of Rochester.

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DOI: 10.1021/acs.joc.5b00380
J. Org. Chem. 2015, 80, 4030−4045