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Diastereoselective Palladium-Catalyzed Formate Reduction of Allylic Carbonates en Route to Polypropionate Systems

Anh Chau,[‡] Jean-François Paquin,[§] and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

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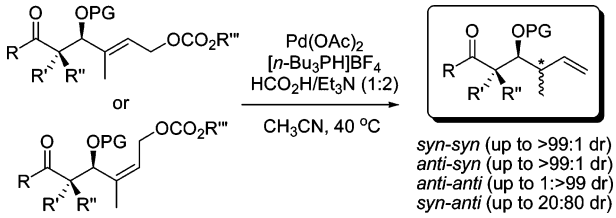

Diastereoselective palladium-catalyzed formate reduction of allylic carbonates presents unique opportunities for applications in target-oriented organic synthesis provided that selectivity, in particular stereoselectivity, in the course of this metal-catalyzed reaction can be controlled. This article describes our recent developments on new and efficient metal-catalyzed processes exploiting resident stereocenters on the substrates as a means to control stereoselectivity en route to preparing propionate units containing an array of stereochemical patterns. In particular, the effect of the protecting group, the stereochemistry of the aldol adduct, neighboring substituents, and the olefin geometry were examined. Strategic choice of the above parameters provides entry into three of the four possible diastereomeric triads, namely *syn-syn*, *anti-syn*, and *anti-anti*. Preliminary results indicate that construction of the *syn-anti* triad is possible, albeit in moderate diastereoselectivity.

Introduction

Polypropionates (characterized by their alternating methyl-hydroxy-methyl substituents) embody an important and diverse class of natural products such as the ionophores and macrolides.[1] In recent years, polypropionate systems have stimulated extensive interest due to their association with a broad spectrum of biologically active targets with proven or potential use in medicine, including those with antibiotic and anti-cancer properties.[2] Thus the rapid and facile assembly of the polypropionate framework would be very practical and beneficial. A large number of methodologies toward these targets have already been developed.[3−5] Nevertheless, more efficient and versatile synthetic strategies are required.

We recently disclosed the application of γ-carboxy-α,β-unsaturated aldehyde **2** as a synthetic equivalent of β,γ-unsaturated aldehyde **5** (Figure 1).[6] In this strategy, the allylic

[‡] Present address: Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe-Claire-Dorval, Québec, Canada H9R 4P8.

[§] Present address: Département de chimie, Université Laval, Québec, Québec, Canada G1K 7P4.

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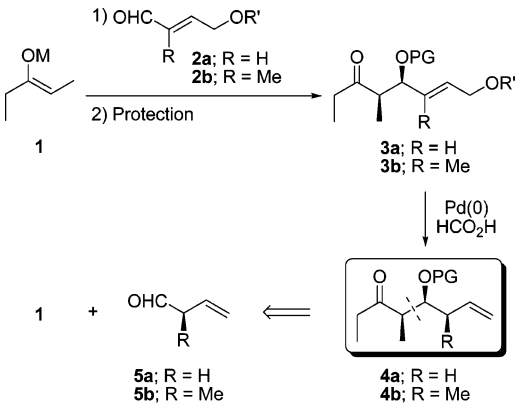
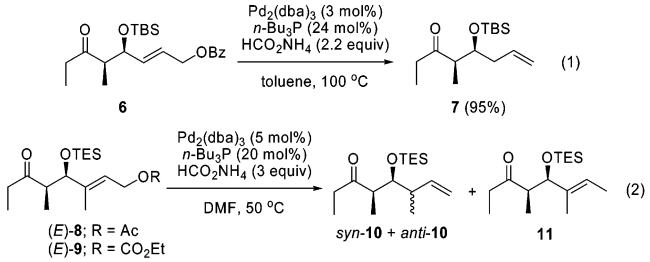


FIGURE 1. Aldol/palladium-catalyzed formate reduction strategy

ester **3** is obtained from an aldol reaction between the corresponding enol ether **1** and α,β-unsaturated aldehyde **2** followed by protection of the alcohol functionality. The key step in this strategy is the palladium-catalyzed formate reduction[7] of **3** that affords our desired products **4** in good yields. Although a direct aldol reaction between enol ether **1** and the β,γ-unsaturated aldehyde **5** could be envisaged to access this class of compounds, this has limited applications. In the case when R = H**,** the β,γ-aldehyde **5a** tends to isomerize to the more stable α,β-unsaturated system; therefore, a 5-fold excess of the aldehyde is required in order to obtain good yields.[8] In the case when R = Me**,** the enantiomerically pure aldehyde **5b** has not been reported and the diastereoselectivity with the racemic aldehyde is modest.[9]

Early experiments in our laboratory demonstrated the potential of this strategy since the reduction of *syn*-aldol adduct **6** under standard palladium-catalyzed reduction conditions furnished terminal olefin **7** in 95% isolated yield as the sole regioisomer (eq 1).[6b] While this result was encouraging, the effect of an alkyl substituent at the vinylic position on the regioselectivity and the ability of such a group to induce diastereoselectivity remained to be investigated. The palladium reduction of this substrate becomes attractive now because it involves the formation of a new stereocenter, affording the possibility of a substrate-controlled diastereoselective transformation. This methodology would prove useful as a new efficient approach to the assembly of stereotriad fragments. In addition, these subunits are particularly versatile as the terminal olefin of these adducts can be further elaborated, both functionally and for chain extension by a variety of protocols. In light of these results, allylic acetate (*E*)-**8** was subjected to similar reduction conditions resulting in alkene *syn*-**10** in good yield (75%) and as a diastereomeric mixture of 5.7:1 in favor of the *syn* isomer, along with 10% of the internal olefin **11** (eq 2).



Whereas a number of investigations have focused on understanding the palladium-catalyzed formate reduction, a search through the literature reveals that few of them have been devoted to this stereoselective approach. While there have been numerous examples of stereoselective palladium-catalyzed formate reductions of allylic moieties, they usually rely on the inversion of an allylic stereocenter[10] or the use of achiral[11] or racemic[12] substrates in conjunction with a chiral ligand. To the best of our knowledge, there are no examples reported in which the stereocenters in this class of substrates have been exploited to influence the differentiation of the two diastereoisomeric palladium π-allyl complexes that are formed upon oxidative insertion of Pd(0).[13] As such, we hoped to look at diastereoselective palladium-catalyzed formate reduction as a stereoselective method and strategy which would provide efficient routes to the construction of stereotriad building blocks **A**−**D** (Figure 2).[14]

Results and Discussion

Optimization Studies. Early efforts focused on optimizing the original reducing system, $Pd_2(dba)_3$ (5 mol %), *n*-Bu_3P (20 mol %), HCO_2NH_4 (2.2 equiv), DMF, 50 °C, using (*E*)-**8** as the reference substrate,[15] by varying different parameters such as the palladium loading (5−20 mol %), the phosphines (*n*-Bu_3P, Ph_3P, Cy_3P, TFP[16]), the concentration (0.1−0.25 M), the Pd:P ratio (2:1 and 1:1), and the temperature (50−70 °C) were unsuccessful. It was surmised that converting to a more reactive leaving group would lead to enhanced diastereoselectivities enabling the reactions to be carried out under milder conditions. Carbonates are known to be excellent leaving groups in π-allyl Pd chemistry,[17] and applying the original conditions in the presence of this moiety ((*E*)-**9**) gave incomplete conversion with a disappointing dr of 75:25. A survey of different solvent systems[18] revealed that acetonitrile was the solvent of choice,

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(8) For aldol reaction with **5a**, see (a) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (b) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119. (c) Crimmins, M. T.; Kirincich, S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *28*, 3675.

(9) For aldol reaction with **5b**, see (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Ahmar, M.; Bloch, R.; Mandville, G.; Romain, I. *Tetrahedron Lett.* **1992**, *33*, 2501.

(10) Bäckwall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335.

(11) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagim, K. *J. Am. Chem. Soc.* **1994**, *116*, 775.

(12) Hayashi, T.; Kawatsura, M.; Iwamura, H.; Yamaura, Y.; Uozumi, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1767.

(13) Tsuji has reported a few examples where reduction of allylic carbonates or formates gave a mixture of diastereomers with modest to no selectivity, see Mandai, T.; Suzuki, S.; Murakami, T.; Fujita, M.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1992**, *33*, 2987.

(14) Review: Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(15) All substrates used in this study are racemic unless noted otherwise. For preparation of substrates see Supporting Information for details.

(16) TFP = tri-2-furylphosphine. For a review on the use of TFP in catalysis, see Anderson, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.

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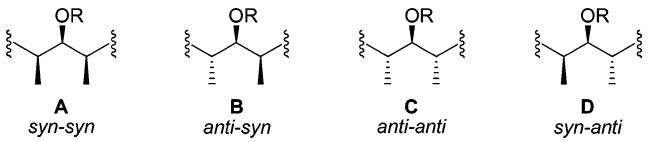


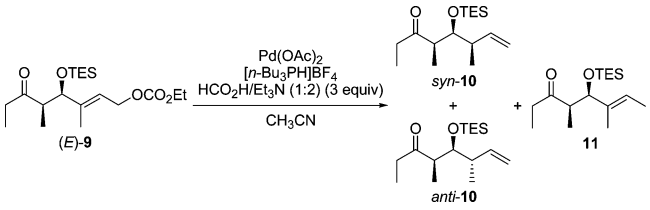
FIGURE 2. Stereotriad building blocks **A**−**D**

increasing the propensity of the starting material to undergo reduction with good conversion and dr > 91:9 at 40 °C or room temperature.

To improve the efficiency of the reaction, as well as resolve some variability problems, alternative palladium and phosphine sources, $Pd(OAc)_2$ and $[n\text{-}Bu_3PH]BF_4$, were investigated, respectively.[19−21] These modifications permitted the number and the nature of the ligands on the Pd center to be controlled,[22] as well as avoiding the use of air-sensitive *n*-Bu_3P. The tetrafluoroborate salt is an air-stable precursor of the phosphine and can be easily liberated under the reaction conditions in the presence of a base. Under the modified conditions, employing 10 mol % $Pd(OAc)_2$, 10 mol % $[n\text{-}Bu_3PH]BF_4$, and 3 equiv of HCO_2H/Et_3N[23] (1:2) at 40 °C in CH_3CN for 5 min gave complete conversion with less than 3% of the internal olefin **11** in a dr of 93:7. A summary of the optimization studies on (*E*)-**9** is presented in Table 1.[24] Using 20 mol % phosphine led to lower conversion with a dr of 83:17 along with 17% of **11**. The absence of a phosphine ligand effectively shuts down the reaction (entry 3), and thus future optimization experiments were performed using a 1:1 ratio of Pd:P. The conversion and the dr were identical whether the reaction was conducted at room temperature or 40 °C (entries 1 and 4). However, running the reaction at 0−5 °C led to incomplete conversion although an excellent dr was obtained (entry 5). Diluting the reaction had a beneficial effect on the diastereoselectivity of the reaction since a ratio of >94:6 was obtained (entry 6). The palladium loading could be decreased to 2.5 mol % (entries 6, 7, 9), consequently increasing the reaction time from 1 to 3 h. The order of addition had some effect since an inverse addition (addition of the catalyst to the reaction mixture) gave good conversion with a dr of 92:8 along with a substantial amount of **11** (entry 8). Furthermore, addition of 1 equiv of Et_3N prior to the formate source and (*E*)-**9** had no effect (entry 10).

Upon scaling up of the reaction, at a 2.5 mol % catalyst loading, heating to 40 °C was necessary to achieve complete conversion within a reasonable time,[25] fortunately without compromising the levels of diastereoselectivity. Optimized conditions, $Pd(OAc)_2$ (2.5 mol %), $[n\text{-}Bu_3PH]BF_4$ (2.5 mol %),[26] HCO_2H/Et_3N (1:2) (3 equiv), CH_3CN (0.05 M), 40 °C, were used for the rest of the study.

TABLE 1. Optimized Catalyst System



entry[b]	Pd loading (mol %)	Pd:P	[conc] (M)	*T* (°C)	conversion[a] 10	11	(*E*)-**9**	dr[c]
1	10	1:1	0.1	40	97	<3	0	93:7
2	10	1:2	0.1	40	83	17	0	83:17
3	10	1:0	0.1	40	0	0	100	
4	10	1:1	0.1	20	97	<3	0	93:7
5[d]	10	1:1	0.1	0-5	50	<3	47	>94:6
6	10	1:1	0.05	20	96	∼4	0	>94:6
7	5	1:1	0.05	20	96	∼4	0	>94:6
8[e]	5	1:1	0.05	20	83	17	0	92:8
9	2.5	1:1	0.05	20	97	<3	0	>94:6
10[f]	2.5	1:1	0.05	20	97	<3	0	>94:6

[a] Estimated by ^1H NMR spectroscopy of crude mixture after workup. [b] 0.1 mmol scale, solution of HCO_2H/Et_3N (1:2) in CH_3CN. [c] See ref 24. [d] Reaction stopped after 8 h. [e] Inverse addition: solution of $Pd(OAc)_2$ and $[n\text{-}Bu_3PH]BF_4$ in CH_3CN was added to a solution of (*E*)-**9** and HCO_2H/Et_3N (1:2) in CH_3CN; [f] Successive addition of Et_3N (1 equiv) and a solution of (*E*)-**9** and HCO_2H/Et_3N (1:1) in CH_3CN to a solution of $Pd(OAc)_2$ and $[n\text{-}Bu_3PH]BF_4$ in CH_3CN.

Influence of the Leaving Group and Protecting Group. To examine the influence of the protecting group and leaving group on the reduction, a series of compounds were prepared with varying steric requirements and leaving group ability (Table 2).[27] Reduction of allylic benzyl carbonate (*E*)-**12** under the optimized conditions proceeded to give the desired product **10** with results identical to those of the ethyl carbonate (entry 2). Alternative leaving groups such as acetate or formate[28] resulted in incomplete conversion (although the dr was >94:6) and no reaction, respectively (entry 3 and 4). The observation that changing the leaving group does not affect the diastereoselectivity supports the reasonable proposal that the ionization is not the selectivity-determining step.

When the reduction was conducted in the presence of a TES or TBS protecting group, the reduced adducts (**10** and **19**) were formed in good yield and high diastereoselectivity (entries 1 and 5). In the case of compound (*E*)-**15** (R = Ac), the desired product **20** was isolated in a moderate yield with a low dr (entry 6), but with selective ionization of the carbonate over the acetate. Treatment of the benzoate ((*E*)-**16**) system under the reaction conditions proceeded in moderate yield and diastereoselectivity (entry 7). Protection as the pivalate ester ((*E*)-**17**), furnished an

(18) Other solvents, including THF, DMF, or a combination of the two, gave lower conversion with low dr.

(19) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513.

(20) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(21) The phosphonium salt can be easily synthesized (see ref 20) or, alternatively, is available from Strem Chemicals.

(22) It was demonstrated that the dba ligands are not fully displaced by *n*-Bu_3P from $Pd_2(dba)_3$ (see ref 19) or by Ph_3P from $Pd(dba)_2$; see (a) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511. (b) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.

(23) Formate salts (HCO_2K, HCO_2Cs) were not as effective, probably due to their low solubility.

(24) The dr (ratio of *syn*/*anti*) of all reactions was estimated by ^1H NMR spectroscopy. For the purpose of this study, >94:6 dr indicates that the other diastereomer was present in less than 6% (typically 4−6%), whereas >99:1 dr specifies that the other diastereomer was not detectable.

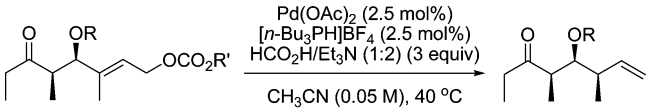
(25) On a 0.2 mmol scale, the reaction with 2.5 mol % Pd at room temperature led to almost complete conversion after 3 days, compared to <1 h at 40 °C. On a 0.5 mmol scale, the reaction with 2.5 mol % Pd is done in <2 h at 40 °C.

(26) A brief screening of ligands ($[Me_3PH]BF_4$, $[Et_3PH]BF_4$, $[i\text{-}Pr_3PH]BF_4$, $[t\text{-}Bu_3PH]BF_4$, and $[Cy_3PH]BF_4$) was carried out to assess the effectiveness of alkyl phosphines in controlling the diastereoselectivity. All gave excellent conversion and dr's, along with variable amounts of the internal olefin. $[n\text{-}Bu_3PH]BF_4$ consistently led to the cleanest reactions, and therefore was used throughout the rest of the study.

(27) Stereochemistry of the products was determined by comparison with authentic samples or similar or previously reported compounds; see Supporting Information for details.

(28) Tsuji has shown that the reduction of formate ester was highly sensitive to the purity of the phosphine and the Pd catalyst, see ref 7c or Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326. It is possible that the presence of amine salts shuts down the reaction.

TABLE 2. Influence of the Protecting Group and Leaving Group



(*E*)-**8**-**9**, (*E*)-**12**-**18** **10**, **19**-**23**

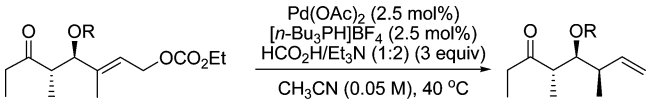
entry	R	R′	substrate	product	yield[a] (%)	dr[b]
1	TES	Et	(*E*)-**9**	10	85	>94:6
2	TES	Bn	(*E*)-**12**	10	85	>94:6
3	TES	Ac	(*E*)-**8**	10	69	>94:6
4	TES	CHO	(*E*)-**13**	10	n/r	nd[c]
5	TBS	Et	(*E*)-**14**	19	85	>94:6
6	Ac	Et	(*E*)-**15**	20	72	58:42
7	Bz	Et	(*E*)-**16**	21	48[d]	80:20[e]
8	Piv	Et	(*E*)-**17**	22	42	>99:1[f]
9	H	Et	(*E*)-**18**	23	60	73:27

[a] Isolated yield. [b] The dr of the isolated product; see ref 24. [c] Not determined. [d] The crude product was contaminated with an unidentified product (18%) and internal olefin (7%). [e] The dr was estimated by ^{13}C NMR spectroscopy. [f] The dr of the crude mixture was 89:11.

89:11 dr in the crude mixture. Fortunately, the major isomer could be isolated by flash chromatography to give **22** in 42% yield and >99:1 dr. The electronic nature of the protecting group seems to have some influence since although it was possible to achieve good diastereoselectivity with some non-silicon based protecting groups, the isolated yields were systematically lower due to side-products formed or unreacted starting material. Subjecting the free hydroxyl under the reaction conditions afforded a lower yield and a modest dr (entry 9).[29,30] Surprisingly, the reduction of the same compound bearing an acetate instead of an ethyl carbonate under the originally reported conditions gave a 1:1 mixture of diastereomers,[6b] whereas a slight preference for the *syn* isomer is observed under our optimized system. From this study, it appears that the protecting group plays an important role in influencing the diastereoselectivity in the course of the formate reduction of these compounds but the cause of this behavior is not fully understood. The *syn*-selectvity of the reaction correlated approximately with the steric demand of the protecting group. Reactions employing bulky silyl protecting groups afforded the highest selectivity, and the dr decreased with diminishing the protecting group size until reaching synthetically useless levels with the free hydroxyl group. In conjunction with a bulky silyl protecting group, such as a *tert*-butyldimethylsilyl, the *syn*-*syn* triad **A** can be accessed in synthetically useful levels of diastereoselectivity using this methodology.

***anti*-*syn* Triad.** The aforementioned results led us to investigate the effect of the relative stereochemistry on the starting allylic carbonates. The results for the reduction of the *anti* aldol adducts (*E*)-**24**−**27** under standard reduction conditions are shown in Table 3. Exposure of (*E*)-**24** with formic acid and triethylamine in the presence of 2.5 mol % of the active palladium catalyst generated from $Pd(OAc)_2$ and [*n*-$Bu_3PH]BF_4$, proceeded to give **28** in good yield (84%) albeit the dr was slightly lower than that for the *syn* diastereomer (*E*)-**9** (entry 1). Congruent with the *syn*-*syn* triad, the use of a large TBS protecting group bestowed better selectivity with a dr of >94:6 as observed from the crude mixture. The minor diastereomer

TABLE 3. Influence of Protecting Group



(*E*)-**24**-**27** **28**-**31**

entry	R	substrate	product	yield[a] (%)	dr[b]
1	TES	(*E*)-**24**	28	84	92:8
2	TBS	(*E*)-**25**	29	46	>99:1
3	TBS	(*E*)-**25**	29	89	>99:1[c]
4	Ac	(*E*)-**26**	30	51	29:71
5	H	(*E*)-**27**	31	63	20:80[d]

[a] Isolated yield. [b] The dr of the isolated product; see ref 24. [c] Reaction was performed using 5 mol % $Pd(OAc)_2$ and 5 mol % [*n*-$Bu_3PH]BF_4$ since some starting carbonate (20−30%) was observed by ^1H NMR when using the standard conditions. [d] Product was contaminated with 25% of the internal olefin.[32]

could be removed by flash chromatography to give **29** in moderate yield (46%) as a single diastereomer along with unreacted (*E*)-**25** (entry 2). The yield could be improved to 85% by increasing the catalyst loading to 5 mol % with equal selectivities (entry 3). This permits access to the *anti*-*syn* isomeric sequence **B**. Interestingly, when (*E*)-**26** or (*E*)-**27** was reacted under the optimal conditions, the *anti* diastereomers *anti*-**30** and *anti*-**31** were formed in moderate yield and low dr (entry 4 and 5). This result is particularly motivating since it opens the way to the synthesis of the *anti*-*anti* triad for which there are limited known methods.[31]

Consequently, a number of different reaction parameters[33] were examined including the palladium:phosphine ratio, concentration, solvent, and nature of the ligand used to optimize for the *anti*-*anti* triad using the free alcohol (*E*)-**27**. Formation of the *anti*-substrate would require delivery of the hydride from the same face as the hydroxy group, perhaps through precoordination. It was hoped that, similar to the well-established hydroxy-directed rhodium-catalyzed hydrogenation of allylic alcohols, substrate direction could provide useful levels of diastereoselectivity.[34] Carrying the reaction out in a nonpolar solvent, such as toluene, indeed gave slightly higher levels of diastereoselectivity (14:86 dr). Unfortunately this was also accompanied by predominant formation of the internal olefin (86%) selectively. Interestingly, the diastereoselectivity was slightly increased by slow addition of the formate source over a period of 8 h to give the desired *anti*-*anti* triad, *anti*-**31**, in 63% yield (13:87 dr) with 35% of the internal olefin. These results suggest that the slow addition extends the lifetime of the palladium π-allyl intermediates to provide a chance for *syn*-*anti* isomerization to occur.

Investigation of the Effect of Olefin Geometry. To date we are able to prepare the stereotriads in greater than 94:6 dr. However, the methodology is restricted to the construction of *syn*-*syn* **A** and *anti*-*syn* **B** stereotriads. Nevertheless, preliminary results indicated that the preparation of *anti*-*anti* stereotriads is also possible for cases where R = H or Ac, albeit in low dr

(29) The diastereomers are separable and the pure *syn* isomer (30%) could be isolated by flash chromatography.

(30) The lack of selectivity observed for the reduction of the free hydroxyl group substrate (*E*)-**23** can be overcome using the chiral (*R*)-MeO-MOP ligand (>96:4 dr).

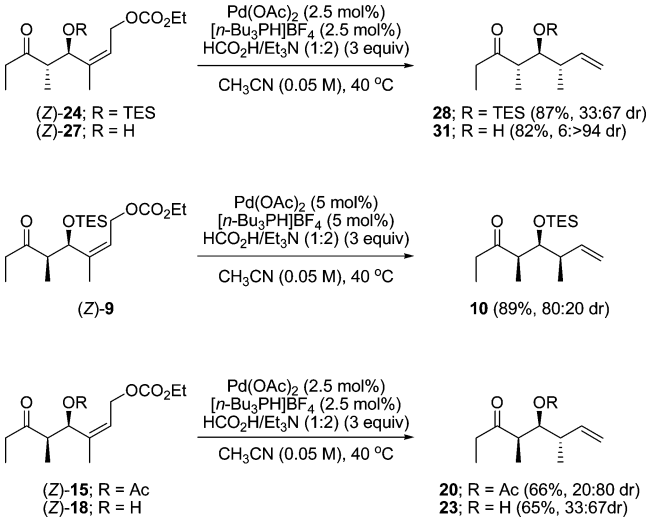
(31) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629 and references therein.

(32) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(33) Solvent: CH_3CN, DMF, THF, DME, dioxane, and toluene. Ligands: [*n*-$Bu_3PH]BF_4$, [$Me_3PhH]BF_4$, [*t*-$Bu_3PH]BF_4$, PPh_3, and TFP. Concentration: 0.025−0.1 M.

(34) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

SCHEME 1. Effect of Double-Bond Geometry

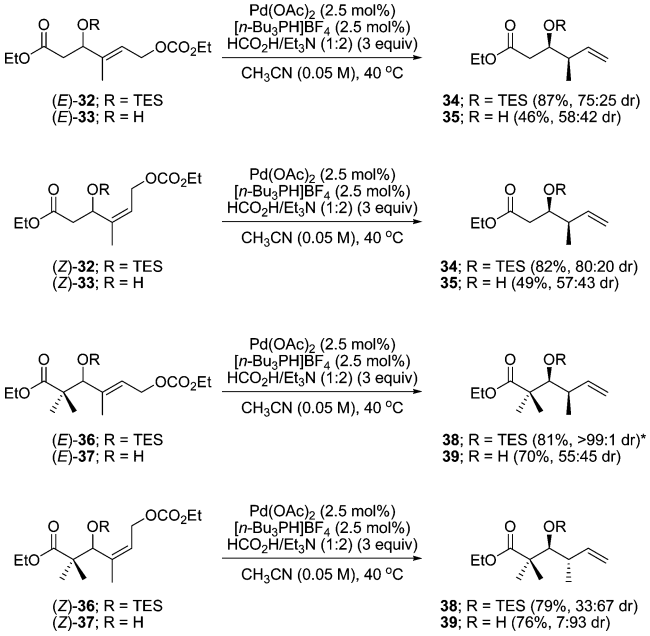


(vide supra). Access to stereotriads **C** and **D** is also important by virtue of their frequent occurrence in polyketide natural products of synthetic interest such as tirandamycin,[35] rifamycin,[36] ionomycin,[37] and denticulatin.[38]

To correct this deficiency, the effect of the olefin geometry on the course of the reaction was probed. From our earlier work, the reduction of TES protected (*E*)-**9** gave >94:6 dr (Table 2, entry 1). Using the conditions applied to (*E*)-**9**, reduction of (*Z*)-**24** gave the propionate system in good yield as a 33:67 diastereomeric mixture (Scheme 1). It is interesting to note that reduction of the (*Z*)-carbonate gives opposite selectivity to that of the (*E*)-carbonate, thereby favoring formation of the *anti* isomer. Gratifyingly, subjecting the free alcohol (*Z*)-**27** to standard formate reduction conditions furnished the *anti*-*anti* triad (*anti*-**31**) in good yield with 6:>94 diastereoselectivity with no trace of the internal olefin isomer, according to analysis of the ^{1}H NMR spectrum. Furthermore, the selectivity could be increased to at least 1:>99 by slow addition of the formate source over 6 h. Under the same reaction conditions, reduction of the (*E*)-configured carbonate (*E*)-**27** gave a dr of 73:27, but was compromised with considerable formation of the internal olefin (Table 2, entry 9). This result further highlights the dramatic influence of olefin geometry in the palladium reduction reaction, whereby incorporation of the (*Z*)-configured olefin into the *anti*-aldol adduct leads to the *anti*-*anti* isomeric sequence **C**.

Accordingly, the (*Z*)-configured *syn* aldol adduct was next investigated. The *anti*-selective reduction of *syn*-aldol adducts is much harder to achieve as these substrates have an intrinsic preference to provide the *syn* triad as a result of steric effects. Diastereoselective formate reduction of *syn* aldol adducts proved more challenging than the previous substrate. The reduction of the (*Z*)-allylic carbonate (*Z*)-**9** using 2.5 mol % of the catalyst system gave incomplete conversion, although **10** was still isolated in 69% with a 80:20 dr. Complete conversion could be achieved by using 5 mol % of the catalyst, and **10** was obtained in 89% yield with the same diastereoselectivity (Scheme 1). Interestingly, when (*Z*)-**15** and (*Z*)-**18** were submitted to the reaction conditions, the *anti* diastereomer was formed in moderate yield and dr.[39,40] In an effort to enhance the stereoselectivity, several different permutations of concentration, solvent, formate (1−10 equiv), phosphine ligands, palladium: phosphine ratio (1:0−1:2), palladium sources ($Pd(OAc)_2$, $Pd_2(dba)_3$), and temperature (−10−80 °C) were evaluated.[33] However, it proved to be unsuccessful. The *syn*-*anti* triad remains the most elusive to obtain in the course of our study. Following this work, the highest selectivity that could be obtained remained a dr of 20:80.

SCHEME 2. Effect of α-Substitution and Geometry of Double Bond



Effect of Substitution. The effects of substitution at the α position, relative to the ketone, on the regioselectivity and diastereoselectivity were next investigated (Scheme 2). Unfortunately, for less sterically biased substrates, low diastereomeric ratios were obtained in the reduction of the free alcohol (*E*)-**33** (58:42 dr). A slight increase in the selectivity was obtained by incorporating a bulky triethylsilyl protecting group which gave **34** in 87% yield with a dr of 75:25.[41] Reduction of (*Z*)-**32** and (*Z*)-**33** gave similar diastereoselectivities to their (*E*)-configured analogues. In both scenarios, irrespective of olefin geometry, the nature of the protecting group had little effect in the absence of the α substituent.

Introduction of a *gem*-dimethyl substituent in the α position significantly increased the dr to >99:1 in the presence of the bulky silyl protecting group ((*E*)-**36**) albeit in moderate yield due to unreacted starting material. The conversion was improved by employing 5 mol % of the catalyst system whereby **38** was obtained in 81% as the *syn* isomer (>99:1 dr). In the absence of this steric bulk ((*E*)-**33**), the dr dramatically decreased to 55:45.[42] These results suggest that the presence of adjacent methyl

(35) Duchamp, D. J.; Branfman, A. R.; Button, A. C., Jr.; Rinehard, K. L. *J. Am. Chem. Soc*. **1973**, *95*, 4077.

(36) (a) Brufani, M.; Cerrini, S.; Fedeli, W.; Vaciago, A. *J. Mol. Biol*. **1974**, *87*, 409. (b) Hanessian, S.; Wang, W.; Yonghua, G.; Olivier, E. *J. Am. Chem. Soc*. **1997**, *119*, 10034 and references therein.

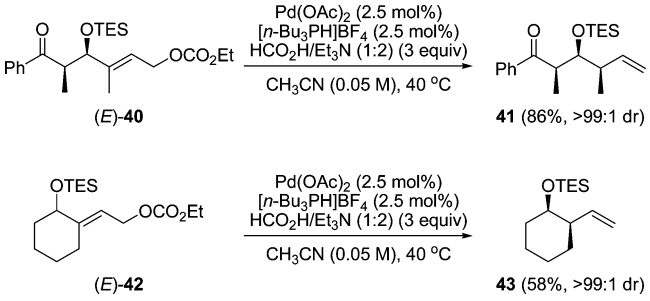
(37) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W.; Gougoutas, J. Z. *J. Am. Chem. Soc*. **1979**, *1015*, 3344.

(38) Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qu-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc*. **1983**, *105*, 7413.

(39) Compound **20** was contaminated with 9% of the internal olefin.

(40) Compound **23** was contaminated with 20% of the internal olefin (*E*/*Z* 1:1).

SCHEME 3. Other Substrates



substituents and a bulky silyl protecting group exerts a significant influence on the stereoselectivity in the reduction.

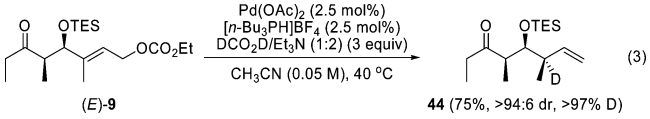
The (*Z*)-double bond geometry, which had been observed to select for the *anti* isomer in previous cases, indeed exhibited a reversal in selectivity. Reaction of a TES protected (*Z*)-**36** yielded a diastereometric mixture of 33:67 in favor of the *anti* isomer. Interestingly, reduction of the free hydroxyl derivative (*Z*)-**37** provided a significantly higher dr of 7:93 in favor of the expected isomer *anti*-**39**. This observation is consistent with the reduction of (*Z*)-**27** above, which also favored the *anti* isomer.

These results indicate the crucial role of the α substituent on the stereoinduction process. Interestingly, diastereoselectivities are almost independent of the olefin geometry in the absence of an α substituent. Along the same lines, increasing the steric bulk of the protecting group favored the *syn* isomer while decreasing the size of the protecting group favored the *anti* isomer. This is operative in all the scenarios discussed. Last, there exists a synergistic relationship between the protecting group and olefin geometry i.e., a large protecting group and (*E*)-olefin geometry is required to select for the *syn* isomer and vice versa.

Preparation of the Other Substrates. All the substrates prepared so far possess a methyl group at the vinylic position in order to afford a propionate moiety after reduction. However, to expand the scope and test the generality of the reaction, we elected to prepare substrates with alternative groups at this position. With the requisite substrates in hand, the effect of the substitution was evaluated, and the results are presented in Scheme 3.[43] Replacing the ethyl group with a phenyl ((*E*)-**40**) has little effect on the reduction, and the selectivity remained at >94:6. Furthermore, the minor diastereomer could be removed by flash chromatography to give **41** in 86% yield as a single diastereomer. The reaction of (*E*)-**42** gave a modest diastereoselectivity of 89:11 as estimated by ^{1}H NMR of the crude mixture. However, similarly, the minor isomer could be removed by flash chromatography to give **43** in 58% yield as a single diastereomer.

Isotopic Labeling. The use of formic acid-d_2 in the palladium-catalyzed formate reduction of allylic systems offers an entry into labeled products having deuterium at the allylic position.[44] Since propionates are an important class of biological molecules and isotopically labeled compounds are frequently used with NMR spectroscopy to get more insight on biological systems,[45] the preparation of isotopically labeled propionate units was attempted.

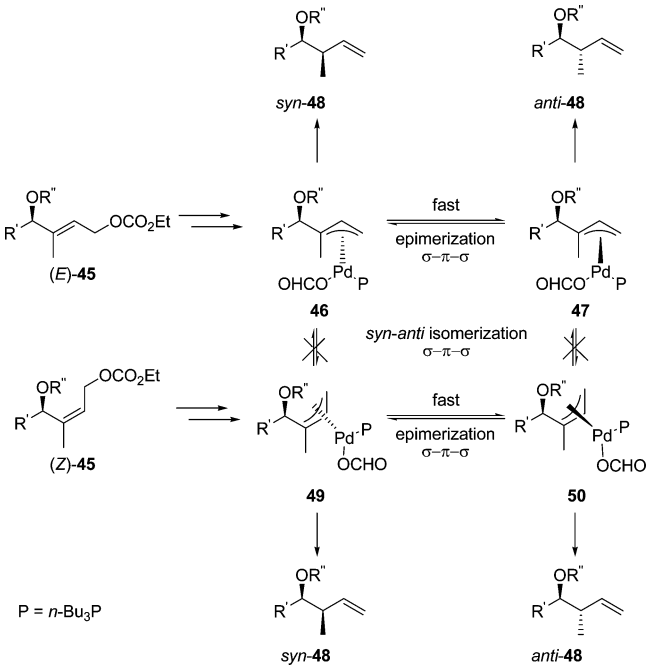
The reaction of (*E*)-**9** using the optimized conditions and DCO_2D in place of HCO_2H gave the desired labeled compound **44** in good yield, excellent diastereoselectivity, and deuterium incorporation (eq 3). The deuterium atom was incorporated only



(3)

at the allylic position, which is evident by ^{1}H and ^{13}C NMR and HRMS.[46] This example shows that the use of formic acid-d_2 allows for the rapid and stereocontrolled preparation of deuterium-labeled propionate fragments.

SCHEME 4. Working Model



Mechanistic Insights. It is not possible with the current information available to propose a definitive model for the reactivity observed. However, some comments about the possible equilibration of the Pd complexes can be made. The working model illustrated in Scheme 4 is based upon proposals described in the literature for this class of substrate.[17b−c,47] The oxidative addition of the palladium catalyst to the allylic carbonates (*E*)-**45** would result in the formation of the π-allyl complexes **46** and **47**. The oxidative addition might occur preferentially from one side of the allylic carbonate. However, this should not affect the outcome since it is believe that **46** and **47** are in rapid equilibration.[48]As first proposed by Hayashi,

(41) Derivatives of this class of compounds have attracted some interest, see (1) (a) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 3588. (b) Alemany, C.; Bach, J.; Garcia, J.; López, M.; Rodríguez, A. B. *Tetrahedron* **2000**, *56*. (c) Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.* **1986**, *27*, 5281.

(42) The product **39** was contaminated with 22% of the internal olefin.

(43) The dr given is for the isolated product, see ref 24.

(44) Hayashi, T.; Iwamura, H.; Uozumi, Y.; Matsumoto, Y.; Ozawa, F. *Synthesis* **1994**, 526.

(45) For examples, see (a) Anglister, J. *Quart. Rev. Biophys.* **1990**, *23*, 175 and references therein. (b) Wade, D. *Chem.-Biol. Interact.* **1999**, *117*, 191 and references therein. (c) Tsuzuki, H.; Tsukinoki, T.; Mataka, S.; Fukata, G.; Ishimoto, K.; Tashiro, M. *Radioisotopes* **1995**, *44*, 929.

(46) The stereochemistry of **44** was assigned based on the selectivity observed with (*E*)-**9** using HCO_2H.

(47) (a) Oshima, M.; Sakamoto, T.; Maruyama, Y.; Ozawa, F.; Shimizy, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 453. (b) Oshima, M.; Shimizu, I.; Yamamoto, A.; Ozawa, F. *Organometallics* **1991**, *10*, 1221. (c) Hutchins, R. O.; Learns, L. *J. Org. Chem.* **1982**, *47*, 4380.

the stereochemical outcome (*syn*-**48** or *anti*-**48**) would be determined by the thermodynamic stability of the epimeric π-allyl palladium intermediates (**46** and **47**).[49] Based on this understanding, since the product *syn*-**48** is the major isomer observed, complex **46** would be the more thermodynamically stable complex.[50] The scenario with the olefinic isomer (*Z*)-**45** could be explained by a similar argument where a mixture of π-allyl palladium complexes would probably be formed upon oxidative addition. However, based on Hayashi's work, *syn*-*anti* isomerization with this class of substrate would be slow compared to reduction.[48] This notion is supported by the fact that the reduction of *E*-olefinic isomers gave products with different diastereoselectivity than the reduction of the analogous *Z*-olefinic isomers. On the basis of our results, we reasoned that when R is a large silyl protecting group, the steric bulk shields one face of the π-allyl complex, forcing the palladium to coordinate from the opposite face and leading to the *syn* diastereoisomer as the major product. When the size of the protecting group is decreased, intermediate **50** may be more favorable due to precoordination of the palladium followed by hydride delivery from the same face of the π-allyl complex to give to *anti* isomer. Although we suggest internal participation of the free hydroxy group, its critical role in the reduction step still remains unclear.

At this stage, it is not possible for us to confidently rationalize the sense of stereoinduction that we observe especially since the exact nature of the reductive decarboxylation is not known.[51] However, one thing that is clear to us is that the reaction itself is multi-faceted and that there is no single controlling element. Our results suggest that the relative configuration of the methyl-hydroxy array obtained from the reduction is controlled by the initial stereogenic centers in the aldol adduct, the nature of the protecting group, nearby substitution, and the geometry of the double bond. These factors all play an important role in determining the conformation[52] of the palladium π-allyl intermediate that subsequently undergoes reduction.

Double Diastereoseletive Palladium-Catalyzed Formate Reduction. With our diastereoselective palladium-catalyzed formate reduction in hand, we considered whether this methodology could serve as a key step toward the construction of building blocks for expedient polypropionate synthesis. We envisaged the target molecule **53** being generated by sequential chain extension in two directions, followed by a double diastereoselective palladium-catalyzed formate reduction (Scheme 5). One of the advantages that would accrue from the development of such a process would be the simultaneous formation of two new stereocenters. These products are synthetically interesting because the terminal olefin functionality provides a handle for additional carbon skeleton-expanding operations and reduction of the ketone moiety permits formation of a seventh stereocenter en route to polypropionate systems.

SCHEME 5. Strategy

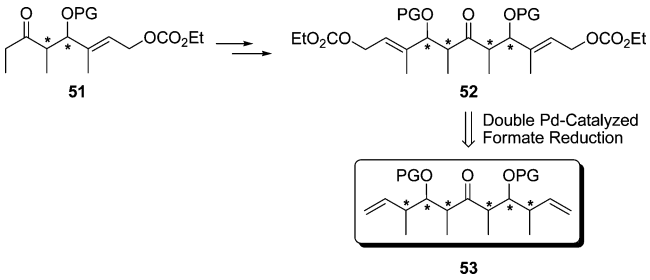
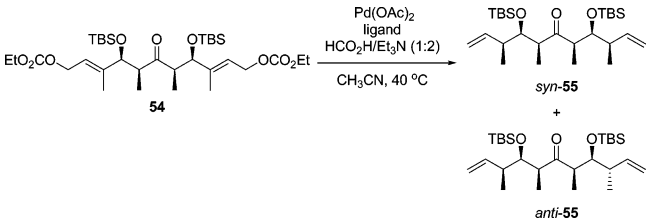


TABLE 4. Selected Results from Optimization of Double Palladium-Catalyzed Formate Reduction



entry[a]	Pd loading (mol %)	Pd:P ratio	formate equiv	[conc] (M)	dr[b]
1	2.5	1:1	3.0	0.05	77:23
2	2.5	1:1	3.0[c]	0.05	86:14
3	2.5	1:2	3.0[c]	0.05	76:24
4	10	1:1	3.0[c]	0.05	76:24
5[d]	2.5	1:1	3.0[c]	0.05	n/r
6	5.0	1:1	3.0	0.05	71:29
7	5.0	1:1	6.0	0.05	60:40
8	2.5	1:1	3.0	0.025	83:17
9	2.5	1:1	3.0[c]	0.025	83:17
10	2.5	1:1	6.0	0.025	64:36
11	2.5	1:1	3.0	0.0125	77:23

[a] See ref 24. [b] Complete conversion was obtained for all the entries except entry 2 (62%). [c] Slow formate addition to substrate and catalyst over 8 h. [d] Room temperature.

With the assembly of the bis aldol adducts,[53] double palladium-catalyzed formate reductions were carried out and a number of different reaction parameters were examined including catalyst, ligand, concentration, and formate equivalents to optimize the diastereoselectivies. Bis carbonate **54** was initially chosen as the reference substrate, as its reduction leads to a *meso* substrate, to simplify our analysis. We felt that the presence of the two functional groups remote from one another would not alter the reaction course. On the basis of this reasoning, we expected nearly no formation of the *anti*-*syn*-*syn*-*syn*-*anti* isomer. Table 4 highlights the preliminary results for the optimization of the all *syn* stereotriad *syn*-**55**. The reduction proceeded smoothly to give the diolefin **55** in 86% yield and with 77:23 diastereoselectivity for the establishment of two new stereocenters (entry 1). Slow formate addition was also found to improve the dr to 86:14, but gave low conversions (entry 2). Unfortunately, attempts to stabilize the catalyst by increasing the phosphine:ligand ratio (entry 3) or increasing the catalyst loadings (entry 4) had a negative effect on the dr. Increasing the equivalents of formate (6.0 equiv, entry 7) had negative effects on the dr. Concentration was found to be important as diluting the reaction by a factor of 2 increased the

(48) It has been shown by Hayashi that the model complex PdCl(η^3-1,1-dimethylallyl)((*R*)-MOP) existed as a mixture of isomers which are in an equilibrium state between −60 °C and 20 °C, see ref 11.

(49) (a) Hayashi, T.; Iwamura, H.; Uozumi, Y. *Tetrahedron Lett.* **1994**, *35*, 4813. (b) Kawatsura, M.; Uozumi, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron* **2000**, *56*, 2247. Also see refs 11, 12, 44.

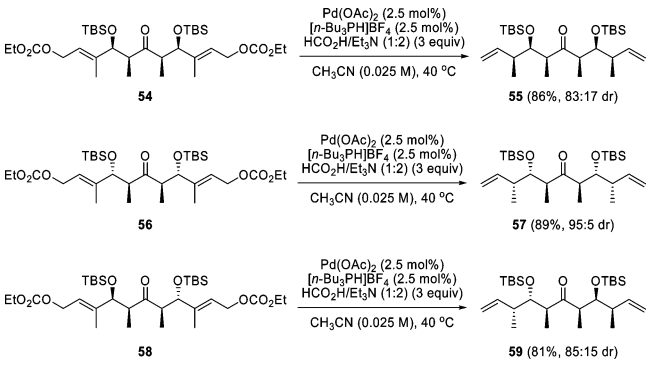
(50) This argument assumes similar rates as in Hayashi's chemistry. If the rate of epimerization is much faster than the reduction, the Curtin−Hammet principle is applicable. In such a case, the *syn*/*anti* ratio is not determined by the relative stability of the π-allyl complexes **46** and **47** but by the relative rate of product formation from each intermediate.

(51) See ref 47a,b and Guibé, F. *Tetrahedron* **1998**, *54*, 2967 and references therein.

(52) For a review of the conformational design, see Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054 and references therein.

(53) Substrates are nonracemic. For preparation of bis aldol adducts, see Supporting Information for details.

SCHEME 6. Double Palladium-Catalyzed Formate Reduction



dr to 83:17 (entry 8). Slow formate addition under optimized concentration (0.025 M) had no effect on the dr (entry 9). Further dilution did not further improve the dr (entry 11).

The three diastereomeric bis aldol adducts were treated under the optimized conditions (i.e. 2.5 mol % $Pd(OAc)_2$, 2.5 mol % [*n*-Bu_3PH]BF_4, and 3 equiv of HCO_2H/Et_3N (1:2) at 40 °C in CH_3CN (0.025 M)) (Scheme 6). The reactions proceeded smoothly to give the reduced adducts in good yields and diastereoselectivities for the establishment of two new stereocenters. Although we have not yet pursued further derivitization of our doubly reduced adducts, additional two-directional applications can be envisioned.

Conclusions. A new approach to propionate units using a diastreoselective palladium-catalyzed formate reduction of allylic carbonates has been developed and can serve as a useful strategy to construct building blocks for polypropionate synthesis. To the best of our knowledge, stereocenters in this class of substrates have never been exploited to control the stereochemical outcome in allylic substitution reactions. Our results indicate the stereoinduction is multi-faceted and is dependent on a number of factors including the nature of the protecting group, nearby substitution, stereochemistry of the aldol adduct, and olefin geometry. Our methodology allows for the preparation of *syn-syn*, *anti-syn*, and *anti-anti* triads in synthetically useful diastereoselectivities. Our preliminary results indicate that the synthesis of the *syn-anti* triad is also possible (dr up to 20:80). Future efforts to devise better solutions to the selectivity problems of the *syn-anti* triad in the reduction reaction seem very much worthwhile.

Experimental Section

General Experimental Methods. See the Supporting Information.

General Procedure for Diastereoselective Palladium-Catalyzed Formate Reduction. To a solution of $Pd(OAc)_2$/[*n*-Bu_3PH]-BF_4 (1:1) (2.5 mol %, 0.06 M/CH_3CN) under nitrogen was added a solution of allylic carbonate (1 equiv) and HCO_2H/Et_3N (1:2) (3 equiv, 1.0 M/CH_3CN) in CH_3CN (0.05 M) via cannula. The resulting mixture was heated to 40 °C until the apparition of black particles (~1 h). H_2O was added, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and brine and dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash chromatography using Et_2O/hexane as an eluant.

(4*R,5*S**,6*R**)-5-Benzoyloxy-4,6-dimethyl-7-octen-3-one (*syn*- and *anti*-21).** Following the general procedure on a 0.20 mmol scale using (*E*)-**16**, the inseparable mixture of diastereomers (26 mg, 48%, 80:20 dr by ^1H NMR spectroscopy) was isolated as a colorless liquid after purification by flash chromatography using 10% Et_2O/pentane. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, m), 7.56 (1H, m), 7.45 (2H, m), 5.84 (1H, ddd, J = 17.2, 10.4, 8.8 Hz, *anti* isomer), 5.76 (1H, ddd, J = 17.2, 10.0, 8.2 Hz, *syn* isomer), 5.50 (1H, dd, J = 8.8, 4.8 Hz, *anti* isomer), 5.46 (1H, dd, J = 8.0, 4.8 Hz, *syn* isomer), 5.12 (2H, m), 2.95 (1H, m), 2.70−2.41 (3H, m), 1.16 (3H, d, J = 7.2 Hz, *syn* isomer), 1.13 (3H, d, J = 7.2 Hz, *anti* isomer), 1.07−1.01 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 166.0, 139.6, 139.1, 133.0, 130.0, 129.7, 128.4, 116.3, 116.1, 76.3, 48.2, 48.0, 41.1, 35.1, 34.4, 17.5, 16.3, 12.9, 10.6, 7.8; IR (neat) ν = 3072, 2977, 2939, 1720, 1452, 1272, 1110, 712 cm^{-1}; HRMS-ES calcd for $C_{17}H_{22}O_3$ $[M + Na]^+$ 297.1461, found 297.1447. The spectral data were identical to an authentic sample (*syn* isomer only) prepared from protection of *syn*-**23** (BzCl, pyridine, CH_2Cl_2, 0 °C to rt) obtained from deprotection of *syn*-**10** (*p*TsOH·H_2O, H_2O, THF).

(4*R,5*S**,6*R**)-4,6-Dimethyl-5-pivaloyloxy-7-octen-3-one (*syn*-22).** Following the general procedure on a 0.20 mmol scale using (*E*)-**17**, the crude product (89:11 dr by ^1H NMR spectroscopy) was purified by flash chromatography using 5% Et_2O/pentane to give *syn*-**22** (22 mg, 42%, >99:1 dr by ^1H NMR spectroscopy) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, ddd, J = 17.1, 10.2, 8.4 Hz), 5.18−5.05 (3H, m), 2.83 (1H, m), 2.63 (1H, m), 2.50−2.32 (2H, m), 1.18 (9H, s), 1.07−0.98 (9H, m); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 211.7, 177.7, 139.6, 116.0, 75.0, 47.8, 40.7, 39.0, 34.3, 27.2, 16.3, 9.8, 7.8; IR (neat) ν = 3078, 2978, 2935, 2874, 1729, 1481, 1460 1281, 1154 cm^{-1}; HRMS-ES calcd for $C_{15}H_{26}O_3$ $[M + Na]^+$ 277.1774, found 277.1780. The spectral data were identical to those of an authentic sample (*syn* isomer only) prepared from protection of *syn*-**23** (PivCl, pyridine, DMAP, CH_2Cl_2, 0 °C to rt) obtained from deprotection of *syn*-**10** (*p*TsOH·H_2O, H_2O, THF).

(4*S,5*S**,6*R**)-4,6-Dimethyl-5-triethylsiloxy-7-octen-3-one (*syn*-28).** Following the general procedure on a 0.20 mmol scale using (*E*)-**24**, *syn*-**28** (48 mg, 92:8 dr by ^1H NMR spectroscopy) was obtained by flash chromatography using 5% Et_2O/hexane as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, m), 5.06 (1H, dt, J = 7.8, 1.5 Hz), 5.01 (1H, d, J = 1.2 Hz), 3.94 (1H, dd, J = 7.8, 3.6 Hz), 2.74 (1H, m), 2.49 (1H, m), 2.31 (1H, m), 0.95 (18H, m), 0.55 (6H, q, J = 7.5 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 214.0, 141.8, 114.5, 77.7, 50.1, 40.7, 36.7, 13.5, 13.1, 7.3, 6.9, 5.2; IR (neat) ν = 3078, 2958, 2874, 1721, 1461, 1378, 1170, 1006 cm^{-1}; MS-EI (*m*/*z*) 255 $[M - Et]^+$, 57 $[C_3H_5O]^+$. The stereochemistry was established by conversion of *syn*-**28** to *syn*-**29** by deprotection (*p*TsOH·H_2O, H_2O, THF) and reprotection (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt).

(4*S,5*S**,6*S**)-5-Acetoxy-4,6-dimethyl-7-octen-3-one (*syn*- and *anti*-30).** Following the general procedure on a 0.20 mmol scale using (*E*)-**26**, the inseparable mixture of diastereomers (22 mg, 51%, 29:71 dr by ^1H NMR spectroscopy) was obtained by flash chromatography using 20% Et_2O/pentane as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, m), 5.14−5.02 (3H, m), 2.85 (1H, m), 2.55−2.36 (3H, m), 2.00 (3H, s), 1.11 (3H, d, J = 6.8 Hz, *syn* isomer), 1.06 (3H, d, J = 7.2 Hz, *anti* isomer), 1.01 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 170.1, 170.0, 139.8, 138.3, 116.1, 115.4, 77.2, 76.8, 48.2, 48.0, 40.0, 38.9, 34.9, 34.7, 20.8, 20.7, 17.5, 13.7, 13.4, 13.2, 7.5; IR (neat) ν = 3072, 2976, 2935, 1746, 1718, 1460, 1374, 1233, 1020 cm^{-1}; HRMS-ES calcd for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ 235.1304, found 235.1293. The stereochemistry was established by comparison with authentic *syn* compound prepared from protection of *syn*-**31** (AcCl, pyridine, CH_2Cl_2, 0 °C to rt) obtained from deprotection of *syn*-**28** (*p*TsOH·H_2O, H_2O, THF).

(4*S,5*S**,6*S**)-5-Hydroxy-4,6-dimethyl-7-octen-3-one (*syn*-31).** Following the general procedure on a 0.21 mmol scale using (*E*)-**27**, **31** (23 mg, 63%, 20:80 dr by ^1H NMR spectroscopy) was obtained by flash chromatography using 30% Et_2O/ pentane as a colorless liquid. Careful flash chromatography using 30% Et_2O/ hexane allows for isolation of a clean sample of *syn*-**31**. ^1H NMR

(400 MHz, $CDCl_3$) δ 5.75 (1H, ddd, J = 16.8, 10.4, 7.6 Hz), 5.04 (2H, m), 3.45 (1H, m), 2.81 (2H, m), 2.61−2.41 (2H, m), 2.30 (1H, quintet, J = 6.8 Hz), 1.17 (3H, d, J = 7.6 Hz), 1.07−1.02 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.6, 141.6, 115.1, 77.4, 47.2, 42.0, 36.2, 14.9, 14.6, 7.3; IR (neat) ν = 3498, 3078, 2976, 2936, 1712, 1459, 1374, 973 cm^{-1}; HRMS-EI calcd for $C_{10}H_{19}O_2$ [M + H]$^+$ 171.1385, found 171.1377. The stereochemistry was established by comparison with authentic *syn* compound prepared from deprotection of *syn*-**28** (*p*TsOH·H_2O, H_2O, THF).

(4*S,5*S**,6*R**)-5-Hydroxy-4,6-dimethyl-7-octen-3-one (*anti*-31).** Following the general procedure (with slow addition of formate over 6 h) on a 0.28 mmol scale using (*Z*)-**27**, *anti*-**31** (39 mg, 82%, 1:>99 dr by ^{1}H NMR spectroscopy) was obtained by flash chromatography using 20% Et_2O/pentane as a colorless liquid. R_f = 0.29 (70% hexanes:ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, ddd, J = 17.0, 10.6, 8.4 Hz), 5.07 (2H, m), 3.62 (1H, ddd, J = 6.2, 3.7, 1.1 Hz), 2.70 (2H, app dq, J = 7.1, 7.1 Hz), 2.62−2.41 (3H, m), 2.33 (1H, m), 1.11 (3H, d, J = 2.6 Hz), 1.09 (3H, d, J = 2.4 Hz), 1.04 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 138.9, 115.7, 77.1, 49.0, 40.9, 35.9, 17.6, 14.1, 7.4; IR (neat) ν = 3462, 3073, 2975, 2937, 1708, 1459, 1376, 971 cm^{-1}; HRMS-EI calcd for $C_{10}H_{19}O_2$ [M + H]$^+$ 171.1386, found 171.1398. The stereochemistry was established by comparison of spectral data above.

Ethyl (3*R,4*R**)-4-Methyl-3-triethylsiloxy-5-hexenoate (*syn*- and *anti*-34).** Following the general procedure on a 0.20 mmol scale using (*E*)-**32**, the inseparable mixture of diastereomers (50 mg, 87%, 75:25 dr ^{13}C NMR spectroscopy) was isolated as a colorless liquid after purification by flash chromatography using 3% Et_2O/hexane. IR (neat) ν = 3077, 2858, 2880, 1739, 1462, 1377, 1180, 1085, 1012 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, m), 5.04 (2H, m), 4.13 (3H, m), 2.38 (3H, m), 1.26 (3H, t, J = 7.2 Hz), 0.98 (12H, m), 0.60 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 140.2, 139.8, 115.3, 114.9, 72.9, 72.4, 60.3, 43.8, 43.7, 40.0, 39.4, 14.9, 14.1, 6.8, 5.0, 4.9; HRMS-EI calcd for $C_{13}H_{25}SiO_3$ [M − Et]$^+$ 257.1573, found 257.1572. The relative configuration was unambiguously deduced after compound **34** was reduced and deprotected (DIBAL, CH_2Cl_2, −78 °C then 10% HCl). ^{1}H NMR of the crude mixture showed a 3:1 dr and the chemical shift of the internal vinyl proton of the minor diastereomer was identical to the previously reported *anti* diastereomer,[54] thus confirming the *syn* configuration for the major diastereomer.

Ethyl (3*R,4*R**)-3-Hydroxy-4-methyl-5-hexenoate (*syn*- and *anti*-35).** Following the general procedure on a 0.21 mmol scale using (*E*)-**33**, the inseparable mixture of diastereomers (17 mg, 46%, 60:40 dr ^{1}H NMR spectroscopy) was isolated as a colorless liquid after purification by flash chromatography using 40% Et_2O/hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.70 (1H, m), 5.12−5.06 (2H, m), 4.21−4.15 (2H, m), 3.93 (1H, m, *anti* isomer), 3.87 (1H, m, *syn* isomer), 2.92 (1H, d, J = 4.4 Hz, *syn* isomer), 2.81 (1H, d, J = 3.6 Hz, *anti* isomer), 2.57−2.26 (3H, m), 1.27 (3H, t, J = 7.2 Hz), 1.08 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.2, 140.1, 139.6, 116.1, 115.7, 71.2, 71.1, 60.7, 43.3, 43.2, 38.7, 15.7, 15.4, 14.1; IR (neat) ν = 3498, 3078, 2979, 2933, 1736, 1374, 1183, 1031, 918 cm^{-1}; HRMS-ES calcd for $C_9H_{16}O_3Na$ [M + Na]$^+$ 195.0991, found 195.0982. The stereochemistry was established by comparison with authentic compound prepared from deprotection of **34** (*p*TsOH·H_2O, H_2O, THF).

Ethyl (3*S,4*R**)-2,2,4-Trimethyl-3-triethylsilyloxy-5-hexenoate (*syn*-38).** Following the general procedure on a 0.20 mmol scale using (*E*)-**36** and a 5 mol % catalyst system, *syn*-**38** (51 mg, 81%, >99:1 dr by ^{1}H NMR spectroscopy) was isolated as a colorless liquid after purification by flash chromatography using 10% Et_2O/pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, ddd, J = 17.2, 10.4, 8.0 Hz), 4.95 (1H, dt, J = 17.2, 1.6 Hz), 4.90 (1H, ddd, J = 10.4, 1.6, 0.8 Hz), 4.07 (2H, q, J = 7.2 Hz), 3.95 (1H, d, J = 4.4 Hz), 2.28 (1H, m), 1.24 (3H, t, J = 7.2 Hz), 1.17 (3H, s), 1.12 (3H, s), 0.98 (12H, m), 0.63 (6H, q, J = 7.6 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.2, 143.0, 113.4, 79.7, 60.2, 48.4, 41.4, 24.7, 29.0, 16.2, 14.0, 7.1, 5.5; IR (neat) ν = 2958, 2878, 1735, 1463, 1264, 1113, 1085, 1006 cm^{-1}; HRMS-ES calcd for $C_{17}H_{34}SiO_3Na$ [M + Na]$^+$ 337.2169, found 337.2174. The stereochemistry was established by comparison with an authentic sample prepared (see Supporting Information).

Ethyl (3*S,4*R**)-3-Hydroxy-2,2,4-trimethyl-5-hexenoate (*anti*-39).** Following the general procedure on a 0.20 mmol scale using (*E*)-**37**, **39** (29 mg, 70%, 55:45 dr by ^{1}H NMR spectroscopy) was isolated as a colorless liquid after purification by flash chromatography using 20→30% Et_2O/pentane. Careful flash chromatography using 20→30% Et_2O/pentane allows for isolation of a clean sample of *anti*-**39**. IR ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (1H, ddd, J = 17.4, 10.2, 9.3 Hz), 5.06−4.97 (2H, m), 4.09 (2H, q, J = 7.2 Hz), 3.41 (1H, dd, J = 8.7, 3.3 Hz), 3.17 (1H, d, J = 8.7 Hz), 2.45 (1H, m), 1.28 (3H, s), 1.26 (3H, t, J = 7.2 Hz), 1.19 (3H, s), 1.10 (3H, d, J = 6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.0, 139.2, 115.6, 80.8, 60.6, 45.6, 40.8, 24.1, 22.1, 19.5, 13.9; (neat) ν = 3479, 3072, 2979, 2928, 1726, 1261, 1138 cm^{-1}; HRMS-ES calcd for $C_{11}H_{21}O_3$ [M + H]$^+$ 201.1485, found 201.1490. The stereochemistry was established by comparison with an authentic sample prepared (see Supporting Information).

(1*R,2*R**)-1-Triethylsiloxy-2-vinylcyclohexane (*syn*-43).** Following the general procedure on a 0.20 mmol scale using (*E*)-**42**, the crude product (8:1 dr by ^{1}H NMR spectroscopy) was purified by flash chromatography using pentane as eluant to give *syn*-**43** (28 mg, 52%, >99:1 dr by ^{1}H NMR spectroscopy) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (1H, m), 4.98 (2H, m), 3.86 (1H, m), 2.10 (1H, m), 1.74−1.59 (4H, m), 1.47−1.22 (4H, m), 0.95 (9H, t, J = 8.0 Hz), 0.57 (6H, q, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 113.6, 70.9, 46.9, 33.5, 26.7, 24.5, 20.8, 6.9, 5.0; IR (neat) ν = 3074, 2935, 2877, 1459, 1238, 1100, 1021, 906, 741 cm^{-1}; HRMS-EI calcd for $C_{12}H_{23}SiO$ [M − Et]$^+$ 211.1518, found 211.1521. The stereochemistry was established by deprotection (*p*TsOH·H_2O, H_2O, THF) and comparison of the crude ^{1}H NMR with known compound.[55]

(4*R,5*R**,6*R**)-6-Deuterio-4,6-dimethyl-5-triethylsiloxy-7-octen-3-one (*syn*-44).** Following the general procedure on a 0.20 mmol scale using (*E*)-**9** and DCO_2D, *syn*-**44** (44 mg, 75%, >94:6 dr by ^{1}H NMR spectroscopy, >97% D) was isolated as a colorless liquid after purification by flash chromatography using 5% Et_2O/pentane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, dd, J = 17.1, 10.5 Hz), 5.05−4.98 (2H, m), 3.96 (1H, d, J = 5.4 Hz), 2.66 (1H, m), 2.48 (2H, q, J = 7.8 Hz), 1.09 (3H, d, J = 6.9 Hz), 1.03 (3H, t, J = 7.8 Hz), 0.97 (3H, s), 0.95 (9H, t, J = 8.1 Hz), 0.60 (6H, q, J = 8.1 Hz); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 214.0, 141.5, 114.5, 76.2, 49.9, 42.5 (very weak t, J = 20 Hz), 35.1, 15.4, 12.3, 7.7, 7.0, 5.3; IR (neat) ν = 3075, 2958, 2871, 1711, 1462, 1098, 739 cm^{-1}; HRMS-ES calcd for $C_{16}H_{31}DSiO_2$ [M + Na]$^+$ 308.2126, found 308.2142.

(2*R*,4*R*,5*R*,7*R*,8*S*,9*S*)-4,8-Bis-(*tert*-butyldimethylsiloxy)-3,5,7,9-tetramethyl-undeca-1,10-dien-6-one (*syn*-55). Following the general protocol (0.025 M) on a 0.304 mmol scale using **54**, **55** was isolated by flash chromatography using 2% Et_2O/hexane as a colorless oil (126 mg, 86%, mixture of diastereomers 83:17 dr). R_f = 0.85 (90% hexanes:ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (2H, ddd, J = 15.0, 9.9, 7.3 Hz), 5.01 (2H, dd, J = 2.4, 1.3 Hz), 4.97 (2H, dd, J = 1.8, 1.1 Hz), 3.96 (2H, dd, J = 4.9, 4.9 Hz), 2.81 (2H, app dq, J = 7.1, 4.6 Hz), 2.20 (2H, m), 1.09 (6H, d, J = 7.1 Hz), 0.98 (6H, d, J = 6.8 Hz), 0.88 (18H, s), 0.07 (6H, s), −0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 141.7, 114.4, 74.9, 48.5, 26.1, 18.4, 15.2, 12.5, −3.8, −4.2; IR (film) ν = 3079, 2958, 2886, 2709, 1834, 1706, 1640, 1472, 1414, 1380,

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1255, 1106 cm^{-1}; HRMS-EI calcd for $C_{23}H_{47}O_3Si_2$ $[M - C_4H_7]^+$ 427.3072, found 427.3064.

(2*S*,4*S*,5*R*,7*S*,8*R*,9*R*)-4,8-Bis-(*tert*-butyldimethylsiloxy)-3,5,7,9-tetramethyl-undeca-1,10-dien-6-one (*syn*-57). Following the general protocol (0.025 M) on a 0.16 mmol scale using **56**, **57** was isolated by flash chromatography using 2% Et_2O/ hexane as a colorless oil (70 mg, 89%, <5% of minor diastereomer by ^1H and ^{13}C NMR). $R_f = 0.85$ (90% hexanes:ether); ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (2H, ddd, $J = 17.4, 10.3, 7.7$ Hz), 4.99 (4H, m), 3.94 (2H, dd, $J = 5.3, 5.3$ Hz), 2.80 (2H, app dq, $J = 7.1, 1.5$ Hz), 2.34 (2H, app dq, $J = 7.0, 6.8$ Hz), 1.14 (6H, d, $J = 7.1$ Hz), 1.02 (6H, d, $J = 6.8$ Hz), 0.89 (18H, s), 0.07 (6H, s), 0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 142.4, 114.5, 77.7, 50.4, 41.9, 26.3, 18.5, 15.9, 12.6, −3.8, −4.1; IR (film) $\nu = 3077$, 2957, 2858, 2709, 1834, 1700, 1640, 1472, 1413, 1377, 1255, 1078 cm^{-1}; HRMS-EI calcd for $C_{23}H_{47}O_3Si_2$ $[M - C_4H_7]^+$ 427.3072, found 427.3064.

(2*S*,4*S*,5*R*,7*S*,8*S*,9*S*)-4,8-Bis-(*tert*-butyldimethylsiloxy)-3,5,7,9-tetramethyl-u ndeca-1,10-dien-6-one (*syn*-59). Following the general protocol (0.025 M) on a 0.14 mmol scale using **58**, **59** was isolated by flash chromatography using 2% Et_2O/ hexane as a colorless oil (53 mg, 81%, 85:15 dr by ^1H and ^{13}C NMR). $R_f = 0.85$ (90% hexanes:ether); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (2H, m), 5.48 (4H, m), 4.07 (1H, dd, $J = 6.1, 3.2$ Hz), 3.97 (1H, dd, $J = 6.6, 4.1$ Hz), 2.88 (1H, m), 2.65 (1H, dq, $J = 7.2, 3.1$ Hz), 2.38−2.17 (2H, m), 1.14 (3H, d, $J = 1.1$ Hz), 1.04−0.99 (9H, m), 0.87 (9H, s), 0.86 (9H, s), 0.10 (3H, s), 0.05 (3H, s), −0.03 (3H, s), −0.05 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 142.2, 141.9, 114.2, 76.8, 73.8, 49.8, 49.0, 43.2, 41.2, 26.2, 26.1, 18.5, 18.2, 15.9, 14.6, 12.5, 11.3, −3.8, −4.0, −4.3; IR (film) $\nu = 3078$, 2957, 2886, 2858, 1711, 1640, 1472, 1413, 1377, 1254, 1104 cm^{-1}; HRMS-EI calcd for $C_{23}H_{47}O_3Si_2$ $[M - C_4H_7]^+$ 427.3072, found 427.3064.

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Supporting Information Available: Experimental procedures, isolation and spectroscopic information, and ^1H and ^{13}C spectra for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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