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Diastereoselective Palladium-Catalyzed Formate Reduction of Allylic Carbonates as a New Entry into Propionate Units

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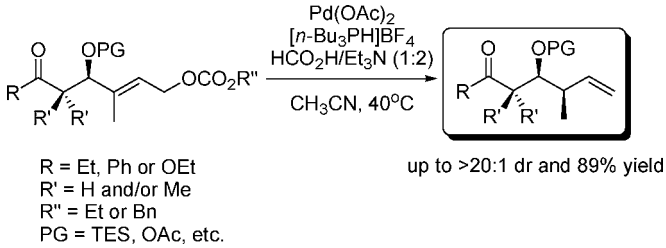
ABSTRACT



The diastereoselective palladium-catalyzed formate reduction of allylic carbonates is described. Reduction of allylic carbonates under mild conditions ($Pd(OAc)_2$ (2.5–5 mol %), [*n*-$Bu_3PH]BF_4$ (2.5–5 mol %), HCO_2H/Et_3N (1:2) (3 equiv), CH_3CN (0.05M), 40 °C) affords the terminal olefin as the syn isomer in good yields and modest to excellent diastereoselectivity. These compounds, which are useful building blocks for the synthesis of polypropionate units, are the synthetic equivalent of the products obtained from an aldol reaction of an α-methyl-*β*,*γ*-unsaturated aldehyde.

We recently reported the use of *γ*-carboxy-α,*β*-unsaturated aldehyde **2** as synthetic equivalent of *β*,*γ*-unsaturated aldehyde **5** (Figure 1).[1] In this strategy, the allylic ester **3** is obtained from an aldol reaction between the enol ether **1** and aldehyde **2** followed by protection of the alcohol functionality. The key step of this strategy is the palladium-catalyzed formate reduction[2] of **3** that affords **4** in good yields. Product **4b** is of interest to us, since a wide variety of natural products contain propionate fragments[3,4] and **4b** is a versatile building block that possesses functional groups useful for further elaboration. Furthermore, direct access by

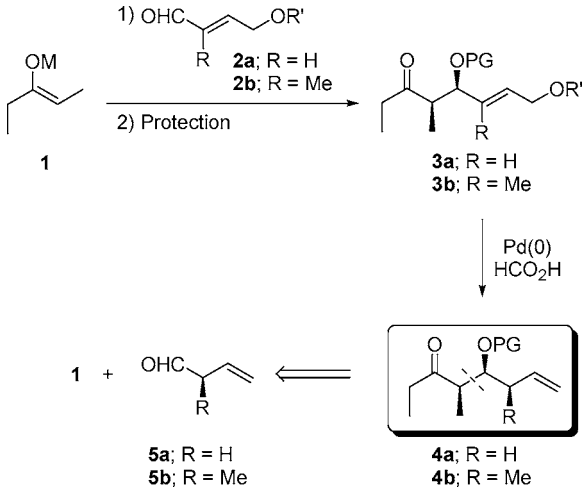


Figure 1. Aldol/Pd-Catalyzed Formate Reduction Strategy

(1) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107.

(2) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1 and references therein. (b) Tsuji, J. Minami, I.; Shimizu, I. *Synthesis* **1986**, 623. (c) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1993**, *49*, 5483. (d) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, *7*, 613. (e) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (f) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195.

(3) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477.

(4) For recent syntheses of propionates containing natural products in our laboratory, see (a) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879. (b) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993.

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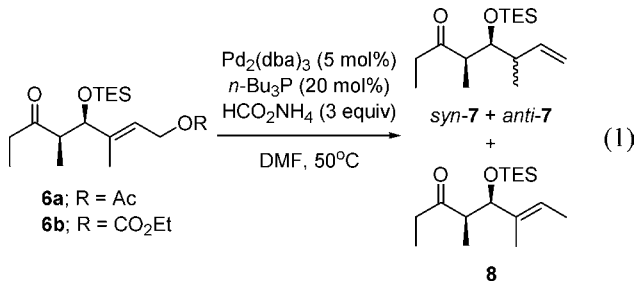
a direct aldol between **1** and α-methyl-β,γ-unsaturated aldehyde **5b** is complicated since the enantiomerically pure aldehyde has not been reported and the diastereoselectivity with the racemic aldehyde is modest.[5]

Early experiments indicated the potential of our strategy since reduction of **6a** gave the desired product **7** in good yield (75%) and moderate selectivity (5.7:1 dr) in favor of the syn isomer along with 10% of the internal olefin **8** (eq 1).[1] In this case, an α-substituted-γ-carboxy-α,β-unsaturated aldehyde is used as a synthetic equivalent of an α-substituted-β,γ-unsaturated aldehyde, which are rarely used in total syntheses[6] primarily because of olefin isomerization.[7]

Even though this strategy allows access to products of broad interest, to be synthetically useful, higher selectivity is needed as well as a determination of the scope of the reaction. We have improved the diastereoselectivity (up to >20:1 dr) by optimizing the reaction conditions, studied the influence of protecting group, leaving group, olefin geometry, and nearby substitution, and report the results of our investigation herein.



(1)

Initial efforts to optimize the original system ($Pd_2(dba)_3$ (5 mol %), *n*-Bu_3P (20 mol %), HCO_2NH_4 (3 equiv), DMF, 50 °C) using **6a**[8] were unsuccessful. We turned our attention to a more reactive leaving group hoping to improve the diastereoselectivity by using milder conditions. Carbonates are known to be an excellent leaving group in π-allyl Pd chemistry,[9] and applying the original conditions to **6b** gave incomplete conversion with a disappointing dr of 3:1. Examination of different media[10] showed that acetonitrile was the solvent of choice and gave **7** with good conversion with dr > 10:1 at 40 °C or room temperature.

To make the reaction simpler to run as well as resolve some variability problems, we decided to employ $Pd(OAc)_2$ and [*n*-Bu_3PH]BF_4 as the palladium and phosphine sources, respectively.[11−13] These changes allowed us to control the number and the nature of the ligands on the Pd center,[14] as well as avoid the use of air-sensitive *n*-Bu_3P since the tetrafluoroborate salt is an air-stable precursor of the phosphine. Under the modified conditions, using 10 mol % $Pd(OAc)_2$, 10 mol % [*n*-Bu_3PH]BF_4, and 3 equiv of HCO_2H/Et_3N[15] (1:2) at 40 °C in CH_3CN gave, after 5 min, complete conversion with less than 3% of the internal olefin **8** in a dr of 13:1. A summary of the optimization studies on **6b** is presented in Table 1.[16] Using 20 mol % phosphine led to lower conversion with a dr of 5:1 along with 17% of **8**. The use of a phosphine is required since no reaction was observed in its absence (entry 3), and a 1:1 ratio of Pd:P was used throughout the rest of the study. The conversion and the dr were identical between room temperature and 40 °C. However, running the reaction at 0−5 °C led to incomplete conversion but an excellent dr (entry 5). Diluting the reaction had a beneficial effect on the diastereoselectivity of the reaction since a ratio of >15:1 was obtained (entry 6). The palladium loading could be decreased to 2.5 mol % (entry 6−8), causing the reaction time to increase from 1 to 3 h.

When the scale was increased, it was found that for a palladium loading of 2.5 mol % running the reaction at 40 °C was required in order to obtain complete conversion in a reasonable time,[17] although no effect on the dr was observed. Optimized conditions [$Pd(OAc)_2$ (2.5 mol %), [*n*-Bu_3PH]-BF_4 (2.5 mol %), HCO_2H/Et_3N (1:2) (3 equiv), CH_3CN (0.05 M), 40 °C] were used for the rest of the study. This study represents the first use of phosphonium salts as a precursor of phosphines in allylic substitution reactions.

The effects of the leaving group and protecting group were also examined (Table 2).[18] Under the optimized conditions, the model substrate **6b** gave 84% yield with a dr of >15:1 with less than 3% of **8**. The substrate bearing a benzyl carbonate (**9**) gave identical results.[19] Using a bulkier TBS group allowed the reaction to proceed in similar yield and diastereoselectivity (entry 3). When R = Ac, the desired product **14** was obtained in lower yield with a low dr (entry

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

(6) For relevant examples of the use of α-substituted-β,γ-unsaturated aldehyde in total synthesis, see: (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. (b) Salamonczyk, G. M.; Han, K.; Guo, Z.-W.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893. (c) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.

(7) For a Lewis-acid-mediated approach to β,γ-unsaturated aldehydes and their reactions in situ, see: (a) Lautens, M.; Maddess, M. L.; Sauer, E. L. O.; Ouellet, S. G. *Org. Lett.* **2002**, *4*, 83. (b) Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079.

(8) All substrates used in this study are racemic.

(9) (a) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*. John Wiley & Sons: Chichester, 1995; pp 290−422. (b) Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 833−884.

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

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

(12) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. The free phosphine is liberated by the action of a base, Et_3N in our case.

(13) Phosphonium salt can be easily synthesized (see ref 12) or, alternatively, is available from Strem Chemicals.

(14) It was demonstrated that the dba ligands are not fully displaced by *n*-Bu_3P from $Pd_2(dba)_3$ (see ref 11) or by Ph_3P from $Pd(dba)_2$; see: Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511. Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168.

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

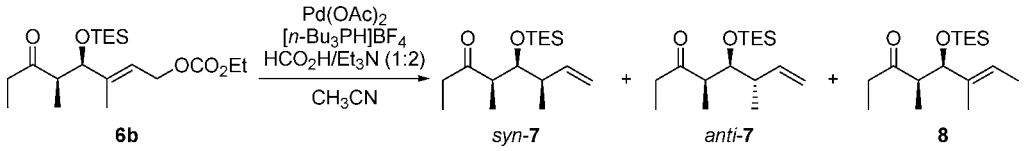
(16) The dr (ratio of syn/anti) of all reactions was estimated by ^1H NMR spectroscopy. For the purpose of this study, >15:1 dr indicates that the other diastereomer was present in less than 6% (typically 4−6%), whereas >20:1 dr specifies that the other diastereomer was not detectable.

(17) 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.

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

(19) Under the optimized conditions, other leaving groups such as acetate or formate (see ref 1c) gave incomplete conversion and no reaction, respectively.

Table 1. Selected Results for the Optimization of the Reduction of Allylic Carbonates

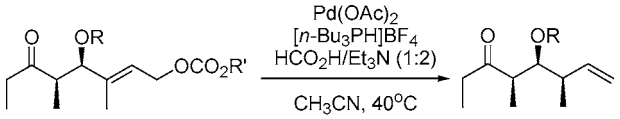


entry[a]	Pd loading (mol %)	Pd:P	concentration (M)	T °C	conversion[b] (%) 7	8	6b	dr[c]
1	10	1:1	0.1	40	97	<3	0	13:1
2	10	1:2	0.1	40	83	17	0	5:1
3	10	1:0	0.1	40	0	0	100	
4	10	1:1	0.1	20	97	<3	0	13:1
5[d]	10	1:1	0.1	0−5	50	<3	47	>15:1
6	10	1:1	0.05	20	96	~4	0	>15:1
7	5	1:1	0.05	20	96	~4	0	>15:1
8	2.5	1:1	0.05	20	97	<3	0	>15:1

[a] Scale = 0.1 mmol. [b] Estimated by ^{1}H NMR spectroscopy of the crude mixture after workup. [c] See ref 16. [d] Reaction stopped after 8 h.

4) but with selective ionization of the carbonate over the acetate. The substrate having a free hydroxyl group was reduced under the reaction conditions although in lower yield and a modest dr (entry 5).[20] Surprisingly, the reduction of **6a** under the originally reported conditions gave a 1:1 mixture of diastereomers, whereas a slight preference for the syn isomer is observed under our optimized system. The protecting groups play an important role in influencing the diastereoselectivity, but the cause of this behavior is not fully understood at this point. Fortunately, the use of a silyl protecting group opens the way to the preparation of the syn−syn triad in synthetically useful levels of diastereoselectivity.

Table 2. Effect of the Leaving Group and Protecting Group



6b; R = TES, R' = Et
9; R = TES, R' = Bn
10; R = TBS, R' = Et
11; R = Ac, R' = Et
12; R = H, R' = Et

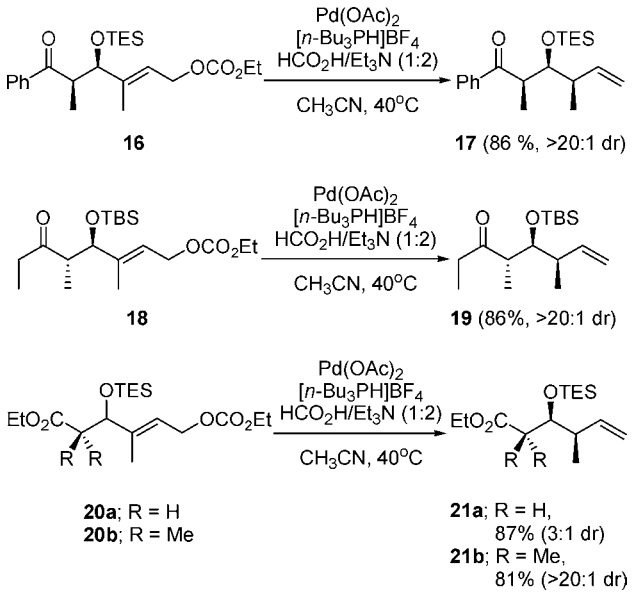
7; R = TES
13; R = TBS
14; R = Ac
15; R = H

entry	substrate	product	yield[a] (%)	dr[b]
1	**6b**	**7**	84	>15:1
2	**9**	**7**	84	>15:1
3	**10**	**13**	85	>15:1
4	**11**	**14**	72	1.4:1[c]
5	**12**	**15**	60	2.7:1

[a] Isolated yield. [b] See ref 16. [c] The dr was estimated by ^{13}C NMR spectroscopy.

The effect of substitution on the substrate was also evaluated as shown in Scheme 1.[18] Replacing the ethyl group with a phenyl had little effect on the reduction since the selectivity was >15:1. In addition, the minor diastereomer could be removed by flash chromatography to give **17** in

Scheme 1. Effect of Substitution



86% yield and >20:1 dr. Similarly, the reduction of the anti diastereomer **18** proceeded in >15:1 selectivity and **19** was isolated as a single diastereomer in 86% yield, opening the way to the synthesis of the anti−syn triad.[21] The substrate lacking a methyl substituent α to the ketone (**20a**) was

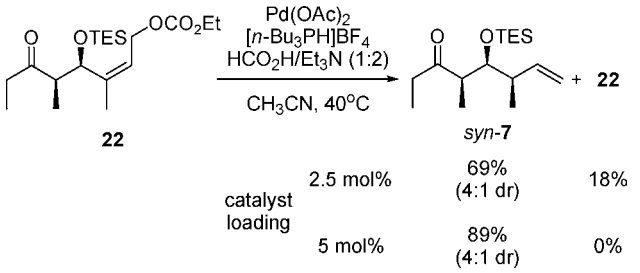
(20) Diastereomers are separable, and the pure syn isomer (30%) could be isolated by flash chromatography.

(21) 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 ^{1}H NMR when using the standard conditions.

reduced in 87% yield but with a modest 3:1 dr,[22] whereas substrate **20b** gave >20:1 dr in 81% yield.[21] These results suggest that substituents on the carbon chain play a role determining the conformation[23] of the π-allyl complex undergoing reduction.

Finally, the geometry of the double bond seems to play an important role since the reaction of the (*Z*)-isomer **22** had to be conducted using 5 mol % catalyst to ensure complete conversion[21] and **7** was isolated in 89% yield with a diastereoselectivity of 4:1 in favor of the syn isomer (Scheme 2).

Scheme 2. Effect of Double-Bond Geometry



This work[1] represents, to the best of our knowledge, the first practical example of diastereoselective palladium-catalyzed formate reduction.[24] Previous stereoselective approaches have been based on the use of chiral phosphine with achiral[25] or racemic[26] allylic acetates or carbonates, or inversion of the allylic stereocenter.[2c,27]

Although the precise mechanism for the hydride transfer has not been clearly established,[28] it is apparent from our work that changes in either the protecting groups or the substitution pattern of the substrates influence this crucial step, and studies are currently underway in order to understand this phenomenon.

In conclusion, we have shown that the diastereoselective palladium-catalyzed formate reduction of allylic carbonates provides access to propionate units including the syn−syn and anti−syn triads. The reaction occurs under mild conditions, and the desired products are obtained in good yields with modest to excellent diastereoselectivity. Our work also shows that α-substituted-γ-carboxy-α,β-unsaturated aldehyde can be used as a synthetic equivalent of α-substituted-β,γ-unsaturated aldehydes.

Extension of this methodology and application to the synthesis of natural products, as well as mechanistic studies, are underway and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Ontario Research and Development Challenge Fund (ORDCF), and the University of Toronto. J.-F.P. acknowledges NSERC, the Fonds québécois de la recherche sur la nature et les technologies, the Walter C. Sumner Foundation, and the University of Toronto for PGS scholarships. We thank Prof. James D. White for kindly providing us with NMR spectra of **13**.

Supporting Information Available: Experimental procedures for the synthesis of the allylic carbonates, general experimental procedures for the formate reduction, isolation and spectroscopic information, and ^{1}H 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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(22) The dr was estimated by ^{13}C NMR spectroscopy

(23) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054 and references therein.

(24) 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.

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(28) (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.