ORGANIC LETTERS

2000
Vol. 2, No. 2
107−110

Use of γ-Carboxy-α,β-unsaturated Aldehydes as Synthetic Equivalents of β,γ-Unsaturated Aldehydes in a Novel Stereoselective Approach to Diketides

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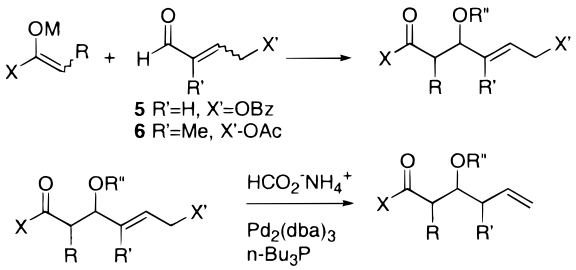
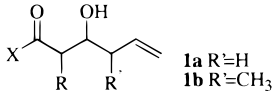
Received October 20, 1999

ABSTRACT



A two-step aldol/Pd-catalyzed formate reduction sequence allows for convenient, stereoselective access to products of great potential in synthetic approaches to polyketides. A novel diastereoselective Pd-catalyzed formate reduction of allylic acetates is reported.

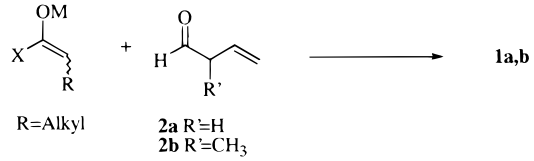
In conjunction with our ongoing studies of diastereoselective ring closing metathesis reactions,[1] we required access to compounds with the general structural features found in **1**.



Perhaps the most direct approach to **1a** or **1b** would involve an aldol reaction between an enolate and a β,γ-unsaturated aldehyde such as **2a** or **2b** (Scheme 1). This strategy has seen limited application,[2,3] particularly in the case of **2b**. The enantiomerically pure aldehyde has not been reported, and the diastereoselectivity of the racemic aldehyde is modest.[3] Crimmins et al. have recently described a convenient approach to **2a** and its use in aldol reactions. Five equivalents of aldehyde per enolate were used, and isolated yields ranging from 25 to 65% were obtained.[2a,4]

We reasoned that substrates such as **1a** and **1b** could be obtained using a two-step procedure involving an aldol reaction between a γ-carboxy-α,β-unsaturated aldehyde such

Scheme 1. Aldol Reactions with β,γ-Unsaturated Aldehydes



(1) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129.
(2) Aldol reactions with **2a**: (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.
(3) Aldol reaction with **2b**: (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Ahmar, M.; Bloch, R.; Mandville, G.; Romain, I. *Tetrahedron Lett.* **1992**, *33*, 2501.
(4) Crimmins, M. T.; Kirincich; S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *28*, 3675.
(5) Synthesis of **4**: Tietze, L. F.; Eicher, T. Syntheses and Transformations of Functional Groups. In *Reactions and Syntheses*; University Science Books: Mill Valley, CA, 1989; Chapter G, p 102.

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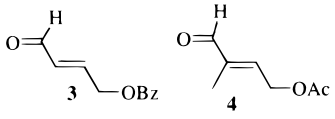
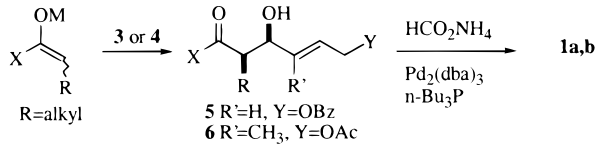
Published on Web 12/29/1999



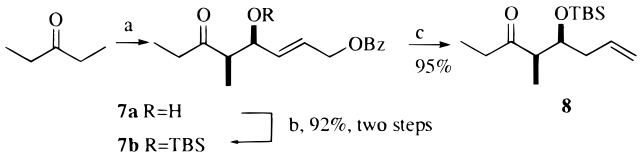
as **3** or **4**,[5] followed by a regioselective Pd-catalyzed formate reduction[6] to yield the desired products **1a** or **1b** (Scheme 2).

Scheme 2. Aldol/ Pd-Catalyzed Formate Reduction Strategy



We began our investigation of the two-step approach using 3-pentanone and **3** as aldol coupling partners. After examining a number of aldol conditions, we found the titanium enolate of the ketone to be most convenient. As might be expected, addition of this enolate to **3** furnished the *syn*-aldol product **7a**,[7] which was silylated to give **7b** in 92% yield over two steps. We were pleased to find that subjecting **7b** to typical formate reduction conditions gave the terminal olefin **8** in 95% yield as a single regioisomer within the detection limits of ^{1}H NMR (Scheme 3).

Scheme 3. Regioselective Formate Reduction of Racemic Aldol Products[a]

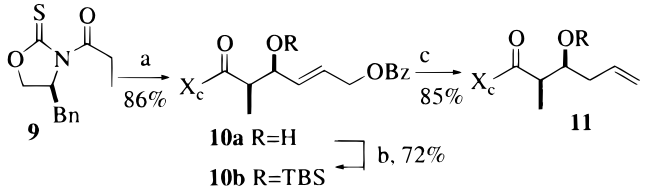


[a] $TiCl_4$ (2.0 equiv), CH_2Cl_2, −78 °C, 10 min; ^{i}Pr$_2$NEt (1.1 equiv), 20 min; **3** (0.5 equiv), 90 min. [b] TBSCl (2.0 equiv), DMAP (0.1 equiv), DMF, 90 min. [c] HCO_2NH_4+ (2.2 equiv), $Pd_2(dba)_3$ (3 mol %), ^{n}Bu$_3$P (24 mol %), toluene, 100 °C, 3 h.

It is important to note that **7a** and **7b** were quite stable and no special precautions were necessary in the isolation of these compounds, which could have been prone to elimination reactions to form conjugated dienones.

We have also used this approach to make nonracemic materials using aldol products formed by coupling the enolate of an oxazolidinethione with **3**. In good agreement with the findings of Crimmins,[8] treating oxazolidinethione **9** with 2.0 equiv of $TiCl_4$, 1.1 equiv of ^{i}Pr$_2$EtN, and 1.1 equiv of **3** afforded an 86% yield of the *syn*-aldol product **10a** (99% yield based on recovered starting material). Silyl ether formation gave the reduction precursor **10b** in 72% yield. We were initially concerned that the presence of the thione might interfere with the Pd-catalyzed formate reduction, but these fears proved unfounded as subjecting **10b** to essentially the same conditions used for the reduction of **7b** gave an excellent yield of the desired terminal olefin **11** (Scheme 4). The progress of the reaction did have to be monitored carefully as extended reaction times gave rise to hydrolysis of the chiral auxiliary.

Scheme 4. Regioselective Pd-Catalyzed Formate Reduction of Chiral Aldol Products[a]



[a] $TiCl_4$ (2.0 equiv), CH_2Cl_2, 0 °C, 10 min; ^{i}Pr$_2$EtN (1.1 equiv), 20 min; **3** (1.1 equiv), −78 °C, 90 min. [b] TBSOTf (1.0 equiv), 2,6-lutidine (1.7 equiv), CH_2Cl_2, −10 °C, 13 h. [c] HCO_2NH_4+ (2.2 equiv), $Pd_2(dba)_3$ (3 mol %), ^{n}Bu$_3$P (24 mol %), toluene, 100 °C, 5 min.

With these encouraging results in hand, we turned our attention to applying this strategy to aldol products formed from aldehyde **4**. The Pd-catalyzed reduction now becomes particularly interesting as it will involve the formation of a new stereocenter, affording the possibility of a substrate-controlled diastereoselective transformation. Such a reaction would afford dipropionates which are of broad interest due to their presence in a large number of natural products. These subunits are particularly versatile as they contain two differentially functionalized termini in the forms of carbonyl and olefin moieties. Independent manipulation of these groups would allow for new propionate units to be attached to either end, and this would represent a new efficient approach to polypropionates.

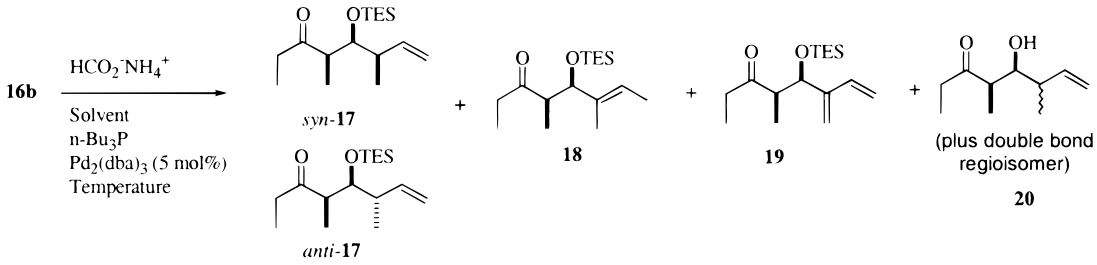
A search of the literature revealed that this type of stereoselective approach has not been previously applied in Pd-catalyzed formate reductions. While there have been numerous examples of stereoselective Pd-catalyzed formate reductions of allylic moieties, they rely on the inversion of an allylic stereocenter[9] or on the use of either achiral[10a] or racemic[10b] allylic acetates and carbonates in conjunction with a chiral ligand. To the best of our knowledge, no examples have been reported which involve the use of a neighboring stereocenter to influence the differentiation between two diastereomeric π-allyl Pd complexes such as *syn*-**14** and *anti*-**14**, which would be formed upon oxidative insertion of Pd(0)

(6) (a) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623.

(7) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(8) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883

Table 1. Diastereoselective Formate Reduction

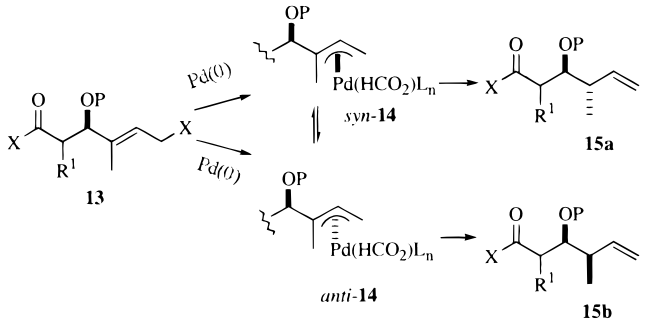


				ratios[a](%)					
run	solvent	temp/time (°C/ h)	P:Pd ratio	**16b**	**17**	**18**	**19**	**20**	dr[a] (*syn*-**17**:*anti*-**17**)
1	toluene	100/ 16	4:1	99					
2	toluene	110/ 16	2:1	0	19	4	77	0	
3	dioxane	100/ 16	2:1	0	0	0	100	0	
4[b]	THF	67/ 16	2:1	65	24	6	5	0	
5	DMF	60/ 18	2:1	10	32	8	0	50	2.7:1
6	DMF	60/18	1:1	5	60	15	0	20	4.9:1
7	DMF	50/18	1:2	5	89 (75)[c]	10	0	<5	5.7:1
8	DMF	60/18	1:4	90	<5	<5	<5	<5	
9	DMF	60/18	0:1	90	0	0	0	0	

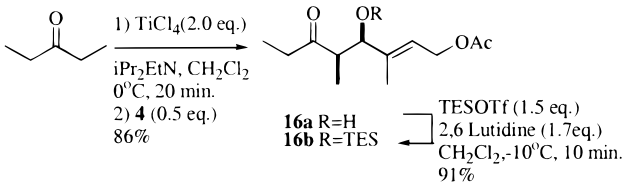
[a] Ratios were determined by ^{1}H NMR of crude reaction mixtures. [b] $HCO_2Et_3NH^+$ was used as a formate source. [c] Isolated yield of *syn*-**17**.

into **13** (Scheme 5). Hydride delivery from *syn*-**14** would give *anti* reduction product **15a**, whereas *anti*-**14** would give rise to the *syn* reduction product **15b**.

Scheme 5. Diastereoselective Pd-Catalyzed Formate Reduction



Aldol additions to aldehyde **4** were performed using the same conditions as employed for aldehyde **3**, so that addition of the titanium enolate of 3-pentanone to **4** (86%) followed by hydroxyl protection as a triethylsilyl ether (91%) gave **16b** in good yield.



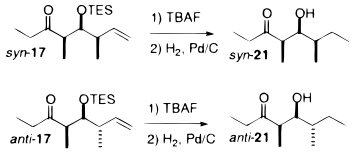
The formate reduction of **16**, however, proved more challenging than previous substrates. Application of the same conditions utilized to reduce **7b** gave a low conversion of **16b** (Table 1, entry 1). A number of different conditions were investigated in an effort to improve conversion of **16b** to **17**. While the use of lower phosphine:Pd ratios did increase the conversion (Table 1, entries 2 and 3), very little of the desired terminal olefin was produced and diene **19** was found to be the major product.[11] While the use of a lower boiling solvent (THF) in conjunction with a more soluble formate source[5b] did improve the ratio of **17**:**19**, the percent conversion was somewhat lower (35%, entry 4). We were encouraged to find that the use of DMF as solvent gave rise to a significant rate acceleration, and complete consumption of **16b** was now observed after 16 h at 60 °C (entry 5). Furthermore, none of the undesired diene product **19** was observed by ^{1}H NMR and a moderate level of diastereo-

(9) (a) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280. (b) Shimizu, I.; Aida, F. *Chem. Lett.* **1988**, 601. (c) Shimizu, I.; Oshima, M.; Nisar, M.; Tsuji, J. *Chem. Lett.* **1986**, 1775. (d) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017. (e) Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1988**, *53*, 3723. (f) Bäckwall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335.

(10) (a) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 775. (b) Hayashi, T.; Kawatsura, M.; Iwamura, H.; Yamaura, Y.; Uozumi, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1767.

(11) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *24*, 2075.

(12) The stereochemistry of the reduction products was confirmed by conversion to known compounds *syn*-**21** and *anti*-**21**. Paterson, I.; Hulme, A. *J. Org. Chem.* **1995**, *60*, 3288.



(13) A similar reactivity has been previously observed: Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589.

selectivity (2.7:1) was observed with the *all-syn* product dominating.[12] The ratio of terminal to internal olefin (**17**:**18**) was 4:1. However, under these conditions, significant amounts of silyl ether hydrolysis (50%) were observed.[13] This is particularly problematic as free alcohol **16a** undergoes Pd-catalyzed formate reduction to give a 1:1 mixture of diastereomers.

The desilylation was found to be dependent upon the phosphine:Pd ratio, so that lowering the ratio to 1:1 (entry 6) resulted in only 20% desilation. A moderate increase in diastereoselectivity (dr = 4.9:1) was also observed. Decreasing the phosphine:Pd ratio even further to 1:2 (entry 7) afforded the optimal conditions for this transformation, giving complete consumption of **16b**, no diene formation, a terminal olefin:internal olefin ratio of 8.9:1, and a dr of 5.7:1. *syn*-**17** was isolated in 75% yield, with <5% of the desilated byproducts being detected by ^{1}H NMR. Further lowering of the phosphine:Pd ratio (entries 8 and 9) resulted in incomplete conversion of starting material.

In conclusion, we have shown that α,β-unsaturated aldehydes **3** and **4** function effectively as replacements in aldol methodologies for β,γ-unsaturated aldehydes **2a** and **2b**. We have also established conditions which allow for good levels of regioselectivity and diastereoselectivity in the Pd-catalyzed formate reduction of allylic acetates to give *syn* reduction products preferentially.

We are currently expanding upon the discoveries presented here and investigating the utility of this sequence in the synthesis of natural products.

Acknowledgment. We thank NSERC Canada, the University of Toronto, and the Merck Frosst Center for Therapeutic Research for financial support. G.H. thanks NSERC for a PGSB fellowship. C.W. thanks NSERC for a UGS award. We are grateful to James Wu for informative preliminary investigations.

Supporting Information Available: Full experimental and analytical data for all new compounds; chemical shifts of peaks used to assign dr's of **17.** This material is available free of charge via the Internet at http://pubs.acs.org.

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