Highly Diastereoselective Rhodium-Catalyzed Hydroformylation of Enol Ethers: A Carbonylation-Based Approach to Catalytic Aldol Synthesis

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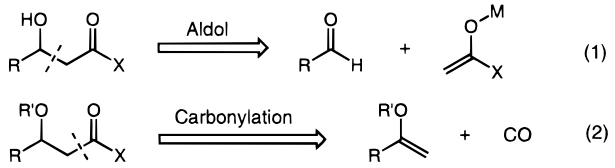
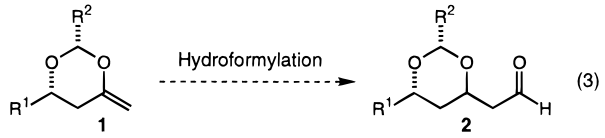
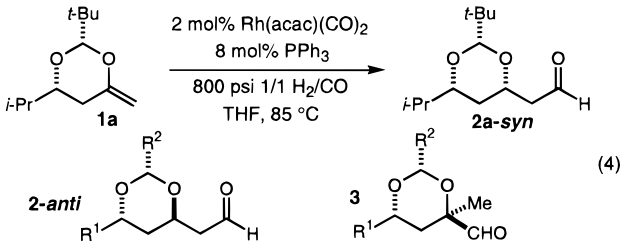
Many methods have been developed for the stereoselective synthesis of (1,3,5,...) polyol chains, a recurring motif in several important classes of natural products.[1] With a notable exception in the work of Rychnovsky,[2] many of these strategies have focused on construction of β-hydroxy carbonyls or their equivalents by way of aldol addition or allylation reactions or related processes.[3,4] These reactions all share in common a focus on construction of the carbon−carbon bond between the hydroxyl-bearing and α-carbons (eq 1). In devising a new catalytic process for the direct synthesis of suitably protected β-hydroxy aldehydes, we wondered whether focus on the carbonyl carbon−α-carbon bond by way of olefin carbonylation might provide an effective approach (eq 2). In principle, the hydroformylation of enol ethers constitutes such an approach. Herein we report that the rhodium (I)-catalyzed hydroformylation of suitably configured enol ethers is an effective method for the highly diastereoselective, catalytic synthesis of β-hydroxy aldehydes.



Despite the vast body of literature on the hydroformylation reaction,[5] examples of enol ethers as substrates are relatively rare.[5c,6] We sought to take advantage of the rigidity imposed by a cyclic system and set as our initial target system the 4-methylene-1,3-dioxanes **1**, prepared by treatment of the corresponding readily available 1,3-dioxanones[7] with Cp_2TiMe_2 after the method of Petasis.[8,9] These enol ethers, we felt, should undergo regioselective hydroformylation, resulting in the direct production of suitably protected 3,5-dihydroxyaldehydes **2** (eq 3).



For our initial attempts at hydroformylation we utilized Rh(acac)$(CO)_2$ (2 mol %) as the catalyst and PPh_3 (8 mol %) as the ligand. Subjection of **1a** (R^1 = *i*-Pr; R^2 = *t*-Bu) to these conditions in THF in a stainless steel pressure reactor (800 psi 1/1 H_2/CO) for 16 h led to the production of aldehyde **2a-*syn*** in 60% yield (eq 4).[9]



No evidence for the presence of the C-3 diastereomer **2a-*anti*** could be detected in the reaction mixture by ^{1}H NMR, and based on GC analysis, we have set 50:1 as a lower limit on the diastereoselectivity of this reaction. The only other product that was produced in a significant amount was regioisomeric aldehyde **3a** (∼5%), also highly diastereoselectively. Thus, although the regioselectivity is ∼12:1, the overall diastereofacial selectivity is remarkably high.

After some experimentation we have discovered that the catalyst loading can be dropped to 1 mol % and the reactions are generally complete within 8 h. The use of the bulky phosphite P(O-*o*-*t*-BuPh)$_3$ as the ligand leads to significantly faster reactions (∼45 min) under otherwise identical conditions in accord with the observations of Van Leeuwen[10] and Claver and Castillón.[6d,e] However, while the diastereoselectivity remains high, we observe a small amount of isomerization of the olefin into the ring with this ligand. Benzene, EtOAc, and THF were all screened as solvent with THF generally giving the cleanest reactions.

Table 1 outlines our results for the hydroformylation of several enol ether substrates. In every case the diastereoselectivity was determined to be at least 50:1 based on GC analysis.[11] Among the key observations is that the bulky *tert*-butyl group in the acetal position is not necessary for high selectivity; indeed, no difference was observed by using the corresponding acetaldehyde-derived acetal (entry 2 vs entry 3). We have also demonstrated some functional group tolerance (entries 4 and 5). Entry 4 is especially noteworthy in the context of (1,3,5,...) polyol synthesis, in that a pseudo-*meso* synthon is produced with the termini differentiated. Finally, we note that the reaction is equally effective on a larger scale with use of 0.50 mol % catalyst (entry 3a).

To understand the origins of the extraordinary diastereoselectivity of these reactions it must first be determined whether insertion of the olefin into the Rh−H bond is irreversible/rate determining. Lazzaroni has documented that this is indeed the

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(3) For recent advances in asymmetric acetate/methyl ketone aldol technology, see: (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8838. (b) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (c) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788−789. (d) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581−8584. (e) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.
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(8) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141−144.
(9) All new compounds were characterized spectroscopically. Stereochemical determinations derived from nOe measurements. Full details are provided in the Supporting Information.
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(11) An independent synthesis of **2-*anti*** was carried out in the case of entry 3. We were thus able to determine a diastereoselectivity of ≥88:1 in this case. See the Supporting Information for details.

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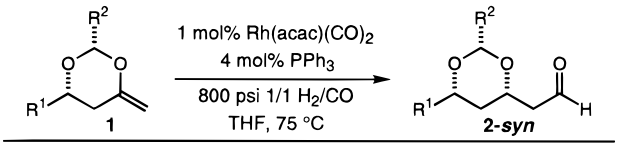
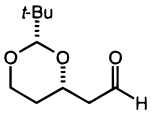
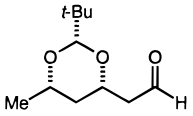
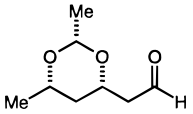
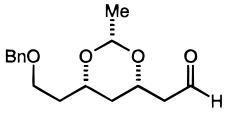
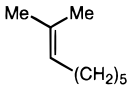
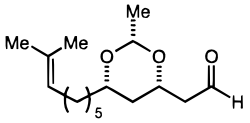
Table 1. Rhodium-Catalyzed Hydroformylation of Enol Ethers[a]



entry	R^1	R^2	major product	yield (%)[b]	rs[c]
1	H	*t*-Bu		81	12:1
2	Me	*t*-Bu		72	13:1
3	Me	Me		75	13:1
3a[d]	Me	Me		80	14:1
4[e]	$BnO(CH_2)_2$	Me		71	9:1
5		Me		71	11:1

[a] All reactions were conducted on a 2.0-mmol scale in 2.0 mL of THF. [b] Isolated yield of major product. [c] Regioselectivity (**2**:**3**) determined by GC analysis of the unpurified reaction mixtures. [d] 21.5 mmol substrate, 0.50 mol % $Rh(acac)(CO)_2$, and 2.0 mol % PPh_3 in 20.0 mL of THF. [e] $P(O\text{-}o\text{-}t\text{-}BuPh)_3$ used in place of PPh_3.

case in the deuterioformylation of ethyl vinyl ether at 20 °C under phosphine/phosphite-free conditions.[6b,12] However, substantial incorporation of deuterium into the enol ether was observed at 100 °C, indicating that olefin insertion is reversible at this temperature. Given the moderately high temperature of our reactions (75 °C) and the presence of PPh_3, we cannot rule out the possibility that olefin insertion is fast and reversible in our system, and the observed selectivity is perhaps due to a thermodynamic preference for the *syn* products. We note as well that deuterioformylation would not be a useful probe in this context for 1,1-disubstituted olefins.

In an effort to distinguish these two mechanistic possibilities we have prepared enol ether **4** carrying an acetonide protecting group. After discovering that hydroformylation of **4** is still *syn*-diastereoselective, producing **5** despite the axial methyl group (Scheme 1), we turned to an investigation of the rate of the reaction. The presence of the axial methyl group should, we

Scheme 1

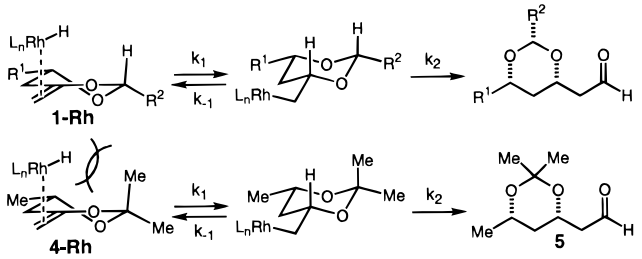
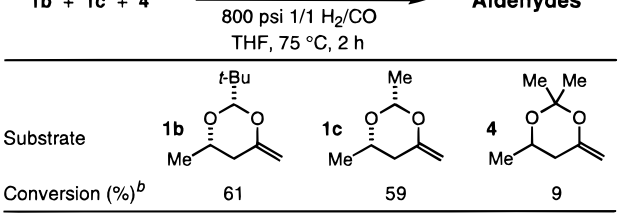


Table 2. Competition Experiment[a]



[a] Experiment performed with 0.67 mmol of each enol ether in 2.0 mL of THF, 1.0 mol % (overall) $Rh(acac)(CO)_2$, and 4.0 mol % PPh_3. [b] Conversion measured by GC analysis of the unpurified reaction mixture with decane as an internal standard.

reasoned, have a deleterious effect on the rate of hydroformylation relative to enol ethers **1** only if olefin insertion is rate determining ($k_2 \gg k_{-1}$), and little or no effect if olefin insertion is fast and reversible and some part of k_2 is rate determining.

Table 2 outlines the results of a competition experiment between enol ethers **1b** (R^1 = Me; R^2 = *t*-Bu), **1c** ($R^1 = R^2$ = Me), and **4** that was analyzed after 2 h. It is clear that the axial methyl group does indeed have a significant effect on the rate of hydroformylation.[13] We believe that this result is most consistent with rate-determining olefin insertion, and by extension that the observed diastereoselectivity is kinetically determined in the olefin insertion step.

Rhodium-catalyzed hydroformylation of 4-methylene-1,3-dioxanes proceeds with good regioselectivity and high diastereoselectivity. The ease of experimental procedure, high diastereoselectivity, and direct production of suitably protected 3,5-dihydroxyaldehydes without the need for functional group manipulation make this an attractive synthetic method. Attempts to extend further the synthetic utility of this process and to understand the mechanistic basis for the selectivity are in progress.

Acknowledgment. We thank Columbia University and the Kanagawa Academy of Science and Technology for their support of this work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (7 pages). See any current masthead page for ordering and Internet access instructions.

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(12) For related mechanistic studies, see refs 6e, 10b, and the following: (a) Stefani, A.; Consiglio, G.; Botteghi, C.; Pino, P. *J. Am. Chem. Soc.* **1973**, *95*, 6504−6505. (b) Consiglio, G. *Organometallics* **1988**, *7*, 778−780. (c) Lazzaroni, R.; Uccello-Barretta, G.; Benetti, M. *Organometallics* **1989**, *8*, 2323−2327. (d) Casey, C. P.; Petrovich, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 6007−6014. (e) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Organometallics* **1997**, *16*, 2981−2986.

(13) Independent experiments confirm that hydroformylation of **4** is significantly slower (<50% conversion after 24 h) than those in Table 1 in the absence of other enol ethers.