Highly Regioselective and Diastereoselective Directed Hydroformylation of Allylic Ethers: A New Approach to Propionate Aldol Synthesis

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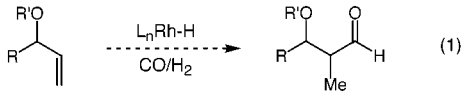
Received August 30, 2001

The rhodium-catalyzed hydroformylation of alkenes is one of the most industrially important reactions and remains one of the most intensely scrutinized reactions in organometallic chemistry.[1] Much of the work has focused on the development of methods for and mechanistic understanding of the selective production of the linear aldehyde regioisomer in the hydroformylation of terminal alkenes. However, the development of methods for the production of the branched aldehyde regioisomer is receiving increasing attention as the efficient synthesis of chiral aldehydes in diastereo- and enantiomerically pure form is of fundamental importance in organic chemistry.

A particularly interesting class of alkenes for the development of a branched-selective hydroformylation is allylic ethers, in that the products of such a reaction would be propionate aldols, a structural subunit contained in numerous bioactive natural products (eq 1). One of the advantages that would accrue from the

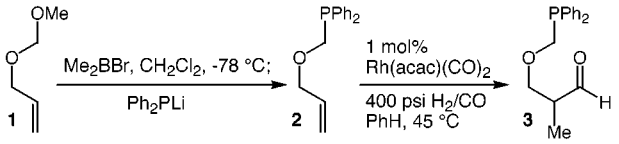


(1)

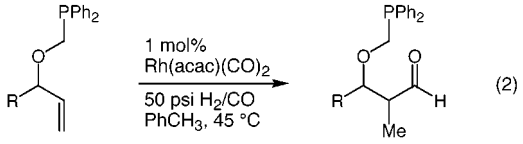
development of such a proces and in contrast to aldol-based methods—is that the products would be protected β-hydroxyaldehydes ready for further chain extension without need for further manipulation. We report herein the first general, *branched-selective* hydroformylation of allylic ethers.

Directing groups have been shown to be an effective method for controlling the course of many reactions,[2] and there have been reports of regio- and diastereoselective hydroformylation reactions based on this concept.[3] More recently, Breit has reported a general and effective method for the linear-selective and diastereoselective hydroformylation of methallyl esters.[4] We envisioned the use of a phosphine directing group tethered to the allylic alcohol substrates through an ether linkage. Early efforts focused on the preparation of diphenylphosphinites; however, subjection of these compounds to standard hydroformylation conditions (Rh(acac)-$(CO)_2$, CO/H_2, PhH, 80 °C) led only to smooth [2,3] rearrangement giving diphenylphosphine oxide products. To avoid this undesired rearrangement pathway, a linking carbon atom was used to join the phosphine with the alcohol of the substrate. Thus, treatment of methoxymethyl (MOM) ether **1** with Me_2BBr followed by $LiPPh_2$ gave the diphenylphosphinomethyl ether **2** (Scheme 1).[5,6] Treatment of **2** with 1 mol % of Rh(acac)$(CO)_2$ and 400 psi of 1/1 CO/H_2 in benzene at 45 °C led to the production of branched aldehyde **3** as a single (>98:2) regioisomer.[6]

Scheme 1



While this result was encouraging, the effect of an alkyl substituent at the allylic position on the regioselectivity and the ability of such a group to induce diastereoselectivity remained to be investigated. Diphenylphosphinomethyl ethers **4** and **5** were therefore prepared (by the same method used in the preparation of **2)** and subjection of these substrates to similar hydroformylation conditions (during these studies it was noted that the pressure could be reduced to 50 psi while still maintaining a reasonable reaction rate) led to the production of aldehydes **6** and **7** with 69:31 and 87:13 diastereoselectivity respectively (eq 2).[6] As in the reaction of **2**, no evidence for the production of any linear aldehyde regioisomer could be detected in either case.



(2)

4 R = Me
5 R = *i*-Pr

6 R = Me, > 98:2 *rs*; 69:31 *ds*
7 R = *i*-Pr, > 98:2 *rs*; 87:13 *ds*

To transform these preliminary results into a more useful process, three issues required attention: (1) the low to moderate diastereoselectivity, (2) the high propensity for air oxidation of the phosphines both in the starting materials and products ($t_{1/2}$ < 5 min), and (3) the development of a method to cleave the diphenylphosphinomethyl ethers. Electronic and steric tuning of the phosphine was pursued in an effort to address the first two of these, and among the phosphines considered for this purpose was the dibenzophosphole group.[7] Thus, dibenzophosphol-5-ylmethyl ether **8** was prepared in 77% yield[8] by using the method described above for the preparation of **2** (Scheme 2). Subjection of **8** to the hydroformylation conditions described above led to the production of aldehyde **9** as a single (>98:2) regioisomer. This reaction was slower than the corresponding reaction of **2**, and thus the catalyst loading was increased to 2.5 mol % and the temperature was increased to 65 °C. A survey of solvents revealed that acetonitrile

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(2) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(3) (a) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237−4240. (b) Jackson, W. R.; Perlmutter, P.; Suh, G.-H. *J. Chem. Soc., Chem. Commun.* **1987**, 724−725. (c) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, 763−764. (d) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31*, 2461−2462. (e) Jackson, W. R.; Perlmutter, P.; Suh, G.-H.; Tasdelen, E. E. *Aust. J. Chem.* **1991**, *44*, 951−966. (f) Jackson, W. R.; Moffat, M. R.; Perlmutter, P.; Tasdelen, E. E. *Aust. J. Chem.* **1992**, *45*, 823−834. (g) van der Slot, S. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2001**, *20*, 1079−1086. (h) Ojima, I.; Zhang, Z. *J. Org. Chem.* **1988**, *53*, 4422−4425. (i) Ojima, I.; Korda, A. *Tetrahedron Lett*, **1989**, *30*, 6283−6286. (j) Ojima, I.; Korda, A.; Shay, W. R. *J. Org. Chem.* **1991**, *56*, 2024−2030. (k) Zhang, Z.; Ojima, I. *J. Organomet. Chem.* **1993**, *454*, 281−289.

(4) (a) Breit, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2835−2837. (b) Breit, B. *Chem. Commun.* **1997**, 591−592. (c) Breit, B. *Eur. J. Org. Chem.* **1998**, 1123−1135. (d) Breit, B.; Dauber, M.; Harms, K. *Chem. Eur. J.* **1999**, *5*, 2819−2827. (e) Breit, B. *Chem. Eur. J.* **2000**, *6*, 1519−1524.

(5) This procedure is adapted from a report on the transformation of MOM ethers to *O*,*S*-acetals. See: Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379−5382.

(6) In these reactions, the products were not purified. The products were obtained with good (>90%) mass recovery, and ^{1}H NMR spectroscopic analysis revealed >90% purity. The relative stereochemistry of the major products was not assigned.

(7) Dibenzophospholes have previously been employed as ligands in transition metal-catalyzed hydroformylation. For lead references, see refs 1b, 1c and: Tóth, I.; Elsevier: C. J.; de Vries, J. G.; Bakos, J.; Smeets, W. J. J.; Spek, A. L. *J. Organomet. Chem.* **1997**, *540*, 15−25.

(8) This yield is artificially low due to volatility of the bromoacetal intermediate. For higher molecular weight substrates the yield in this reaction is typically >90%. See the Supporting Information for details.

10.1021/ja016978t CCC: $20.00
Published on Web 10/30/2001

Scheme 2

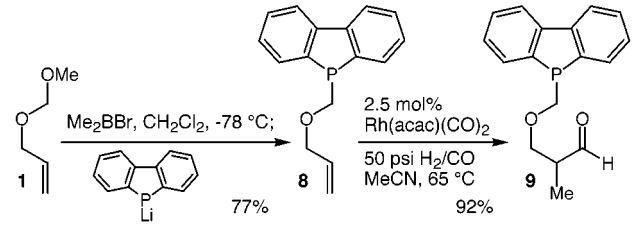
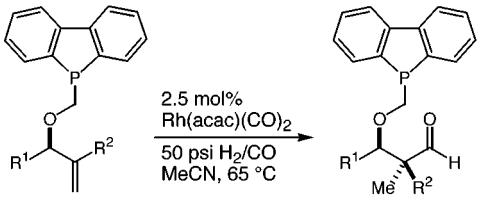


Table 1. Directed Hydroformylation of Dibenzophosphol-5-ylmethyl Ethers of Allylic Alcohols



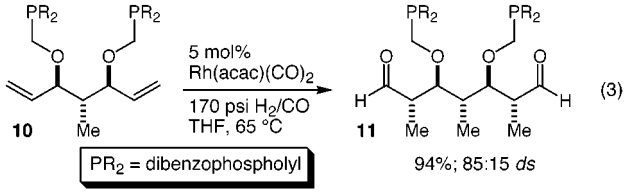
entry	R^1	R^2	rs[a]	ds[b]	y (%)[c]
1	Me	H	>98:2	81:19	92
2	Ph	H	>98:2	86:14	96
3	*i*-Pr	H	>98:2	94:6	94
4[d]	EtO_2C, Me	H	>98:2	90:10	98
5	TBDPSO, Me	H	>98:2	93:7	87
6[e]	H	Me	92:8	-	88

[a] Regioselectivity (branched:linear), as determined by ^{1}H NMR spectroscopy. [b] Diasteroselectivity (anti:syn), as determined by ^{1}H NMR spectroscopy. [c] Isolated yield of the mixture of aldehydes. [d] Reaction run with 5.0 mol % $Rh(acac)(CO)_2$ in THF at 170 psi of H_2/CO. [e] Reaction run with 5.0 mol % $Rh(acac)(CO)_2$ and 1000 psi of H_2/CO at 90 °C.

and THF consistently led to the cleanest reactions and were therefore adopted as the solvents of choice. Under these optimized conditions **9** could be obtained in 92% yield. Importantly, it was observed that both **8** and **9** showed a greatly reduced propensity (relative to compounds **2**−**7**) for air oxidation and could briefly be handled in air with only minimal (<5%) oxidation to the corresponding phosphine oxides.

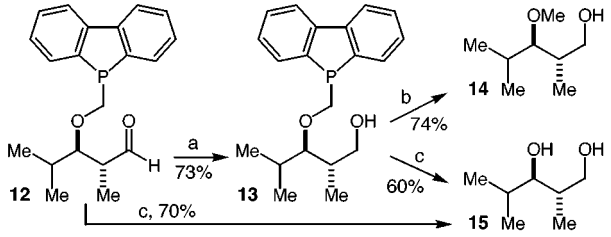
A brief survey was carried out to assess the effectiveness of the dibenzophosphol-5-ylmethyl group in controlling both regio- and diastereoselectivity (Table 1). With a methyl group as the allylic substituent (entry 1), a substantial increase (relative to substrate **4**) in the diastereoselectivity was observed. As the steric size of the allylic substituent was increased (entries 2 and 3), a corresponding increase in the diastereoselectivity was observed, with *i*-Pr resulting in a highly (94:6) diastereoselective reaction. Interestingly, the major product was determined to have the anti relative configuration. Two additional highly diastereoselective reactions (entries 4 and 5) demonstrate tolerance of ester and silyloxy functionalities, as well as relevance to polypropionate construction. Finally, a 1,1-disubstituted olefin was employed as a substrate (entry 6). Remarkably, the branched (quaternary) aldehyde product was obtained with 92:8 regioselectivity. We are aware of no other example of a highly branched-selective hydroformylation of a 1,1-dialkyl-substituted olefin.

Bisdibenzophosphol-5-ylmethyl ether **10** was prepared to investigate the use of this reaction in a two-directional synthesis.[9] We felt this would be a nontrivial extension in that the presence of two phosphines in relatively close proximity could alter the reaction course. Although some optimization was required, hydroformylation of **10** proceeded smoothly to give dialdehyde **11** in 94% yield[10] and with 85:15 diastereoselectivity for the establishment of two new stereocenters (eq 3). This level of selectivity is roughly that expected based on analogy to entry 5, Table 1, and although we have not yet pursued further derivitization of **11**, additional two-directional applications can be envisioned.



After some experimentation we have discovered two reductive methods for cleavage/removal of the dibenzophospholyl directing group. Aldehyde **12** was the starting material for these experiments and it seemed prudent first to reduce the aldehyde to give **13** (Scheme 3). Treatment of **13** with lithium di-*tert*-butylbiphenylide produced methyl ether **14** in 74% yield. In this fashion, differentiation of the two alcohols can be maintained. Alternatively, reduction of **13** with $LiAlH_4$ in dioxane at 150 °C led to complete removal of the directing group to give diol **15** in 60% yield. After optimization of this procedure, it was discovered that aldehyde **12** could be reduced directly to diol **15** in 70% yield.

Scheme 3[a]



[a] Conditions: (a) $LiAlH_4$, THF, −78 °C. (b) Lithium di-*tert*-butylbiphenylide, THF, −78 °C. (c) $LiAlH_4$, dioxane, 150 °C, sealed tube.

An effective directing group strategy for the branched-selective hydroformylation of allylic ethers has been defined. The reactions are highly efficient delivering protected β-hydroxyaldehydes directly from readily prepared substrates with good to excellent diastereoselectivity and in high yield. Two complementary reductive methods for the cleavage of the directing group have been developed. Further studies will seek to exploit this powerful directing effect in the unusual ways.

Acknowledgment. Financial support was provided by the National Institutes of Health (National Institute of General Medical Sciences, GM58133). We are grateful to Bristol-Myers Squibb for generous financial support in the form of an Unrestricted Grant in Synthetic Organic Chemistry to J.L.L. We thank Merck Research Laboratories and DuPont Pharmaceuticals for generous financial support. J.L.L. is a recipient of a Sloan Research Fellowship, a Camille Dreyfus Teacher-Scholar Award, an Eli Lilly Grantee Award, an AstraZeneca Excellence in Chemistry Award, and a GlaxoWellcome Chemistry Scholar Award.

Supporting Information Available: Experimental procedures and characterization data for all substrates and products in Table 1 and **8**−**11**, **14**, and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016978T

(9) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563−566.

(10) This value is the yield of unpurified material after correcting for the mass of the catalyst used. Attempts to purify **11** by chromatography on silica resulted in extensive decomposition.