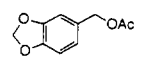
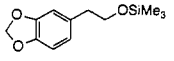
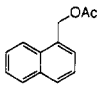
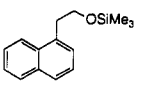
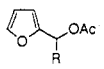
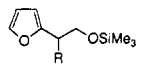
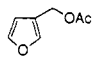
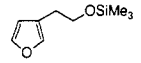
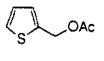
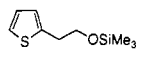
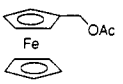
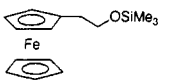
Table I. The $Co_2(CO)_8$-Catalyzed Reaction of Various Benzylic Acetates with $HSiMe_3$ and CO[a]

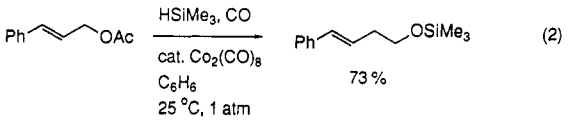
run	substrate	product	time, h	yield, %[b]
1			20	70
2			72	70
				
3	R = H		7	75
4	R = Me		20	79 (72)
5	R = Et		20	74 (59)
6	R = Bu		20	93 (81)
7			72	77
8			20	77 (59)
9			17	(83)

[a] Reaction conditions: benzylic acetate (2.5 mmol), $HSiMe_3$ (25 mmol, 2.9 mL), $Co_2(CO)_8$ (0.1 mmol, 34 mg), benzene (5 mL) at 25 °C under CO (1 atm). [b] GC yields based on benzylic acetate. Isolated yields are in parentheses.

The reaction of benzyl alcohol with $HSiMe_3$[6] and CO in the presence of $Co_2(CO)_8$ did not lead to incorporation of CO and the only product obtained was the trimethylsilyl ether of benzyl alcohol. It was found, however, that benzyl esters reacted catalytically with $HSiMe_3$ and CO to afford trimethylsilyl ethers of β-phenethyl alcohol **2** (benzyl acetate, reaction time 5 days, 43% yield; benzyl formate, 8 days, 44%; benzyl trifluoroacetate, 2 days, 0%).[7,8] Benzyl methyl ether also gave similar results (7 days, 60%). Because of their availability, acetates were chosen as substrates for further study.

The catalytic reaction of eq 1 gave better results for benzyl acetates **1** bearing electron-donating substituents (**2**, R = *p*-OCH_3, 76% yield, reaction time 17 h; R = *o*-CH_3O, 79%, 12 h; R = *p*-CH_3, 75%, 2 days; R = *o*-CH_3, 75%, 3 days; R = H, 43%, 5 days; R = *p*-Cl, 52%, 5 days; R = *p*-CN, 0%, 2 days). Apparently, the development of positive charge seems important at the step in which the carbon–oxygen bond is cleaved by $R_3SiCo(CO)_4$, which could be a key catalyst species.[9] Once alkylcobalt intermediate **3**[10] is formed, it is transformed into **2** successively via acylcobalt carbonyl and aldehyde intermediates (Scheme I).[11]

The new catalytic reaction was applicable to various benzylic acetates, and the results are summarized in Table I. The reaction tolerated functional groups such as methylenedioxy (run 1), furanyl (runs 3–7), and thiophenyl (run 8) groups. Even a ferrocenylmethyl acetate underwent homologation in good yield (run 9). The dicobalt hexacarbonyl complex of propargyl acetate, however, gave a mixture of many products. Under these mild reaction conditions, the acetates of secondary alcohols also gave good yields of the homologated products without competitive β-hydride elimination from the corresponding secondary alkylcobalt intermediates (runs 4–6).[12] The present homologation method also applicable to cinnamyl acetate as shown below (eq 2).



(2)

Further application of this straightforward and unique method for homologation is in progress.

Acknowledgment. This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan. We greatly thank Professor Noboru Sonoda for stimulating discussions.

Supplementary Material Available: Typical experimental procedures and spectral data for products (9 pages). Ordering information is given on any current masthead page.

(6) We have designed a special apparatus for handling the volatile $HSiMe_3$, (bp 6–7 °C). See ref 5.

(7) All new compounds obtained gave satisfactory spectra and analytical (C, H) data; see the supplementary material.

(8) The major side reactions are hydrogenation to toluene and two-carbon extension reactions leading to $PhCH_2CH(OSiMe_3)CH_2OSiMe_3$ and $PhCH_2CH(OSiMe_3)=CHOSiMe_3$.

(9) The reaction of $HSiR_3$ and $Co_2(CO)_8$ has been known to give $R_3SiCo(CO)_4$. Chalk, A. J.; Harrod, J. F. *J. Am. Chem. Soc.* **1967**, *89*, 1640. Baay, Y. L.; MacDiarmid, A. *Inorg. Chem.* **1969**, *8*, 986. Sisak, A.; Ungvary, F.; Marko, L. *Organometallics* **1986**, *5*, 1019.

(10) Benzylcobalt carbonyl compounds are known: Galamb, V.; Palyi, G.; Ungvary, F.; Marko, L.; Boese, R.; Schmid, G. *J. Am. Chem. Soc.* **1986**, *108*, 3344 and references cited therein.

(11) This proposal is based on observations in our previous work on the catalytic reaction of oxiranes with $HSiR_3$ and CO. See ref 5.

(12) A stereochemical test using optically pure (*R*)-α-methyl-2-furfuryl acetate (cf. run 4) showed 56% inversion in accordance with a transition state with carbenium ion character. Efforts to improve the optical yield are now in progress. We gratefully acknowledge Professors Fumie Sato and Yuichi Kobayashi for a gift of the above mentioned chiral acetate. Cf.: Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085.

A Stereospecific Synthesis of 3,3-Disubstituted Allylic Alcohols. The Intermolecular Pinacol Cross-Coupling Reaction between α,α-Disubstituted α-(Diphenylphosphinoyl)acetaldehydes ($Ph_2P(O)CR^1R^2CHO$) and Saturated Aldehydes

Jeonghan Park and Steven F. Pedersen*

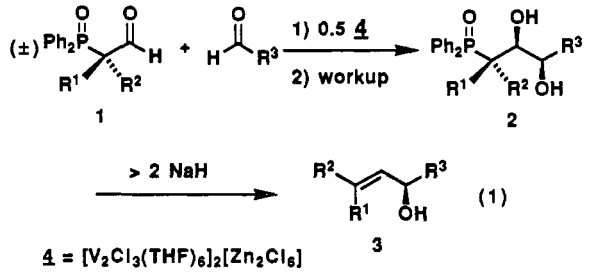
Department of Chemistry, University of California, Berkeley, California 94720

Received July 5, 1990

Summary: High diastereofacial selectivity is observed in the intermolecular pinacol cross-coupling of α,α-disubstituted α-(diphenylphosphinoyl)acetaldehydes with saturated aldehydes. The diols obtained from these reactions are converted to (*E*)-allylic alcohols via a Horner–Wittig elimination reaction.

0022-3263/90/1955-5924$02.50/0

Phosphorus-based methods leading to the stereospecific synthesis of 2,3-disubstituted allylic alcohols are well recognized.[1] Similar routes to the isomeric 3,3-disubstituted analogues (3) are less efficient, especially when the two substituents are similar in size.[1a] Considering the importance of allylic alcohols in a variety of organic transformations,[2] a general route to 3,3-disubstituted isomers would be useful.[3] Furthermore, they are common subunits in several classes of natural products.[4] We envisioned a synthesis of these alcohols using the intermolecular pinacol cross-coupling reaction[5] shown in eq 1,

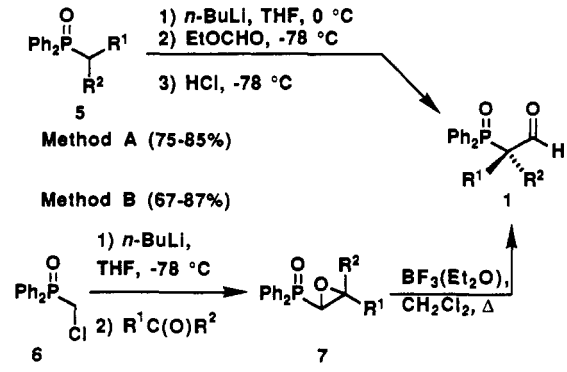


followed by a Horner–Wittig elimination from diol 2. In order for this approach to be considered general and practical, three important requirements must be satisfied. First, efficient syntheses of the aldehydes 1 must be available. Second, the intermolecular pinacol cross-coupling reactions must proceed in high yield. Finally, the reactions must exhibit high diastereofacial selectivity for a range of different sized substituents in 1 (i.e. R^1 and R^2). These goals have been achieved and utilization of the reaction outlined in eq 1 is described below.

Two approaches to the synthesis of the α-(diphenylphosphinoyl)acetaldehydes are shown in Scheme I. The diphenylphosphine oxides (5) used in method A were typically prepared from hydrolysis of the corresponding alkyltriphenylphosphonium salts with sodium hydroxide.[6] Formylation of 5 was accomplished with ethyl formate (*n*-BuLi, −78 °C).[7,8] Method B provides an alternative and potentially more general route to 1. Beginning with the known (α-chloromethyl)diphenylphosphine oxide 6,[9] epoxide 7 was obtained using a procedure analogous to that reported for phosphonate esters.[7] The crude epoxide was then rearranged employing $BF_3(Et_2O)$ (0.5 equiv) in refluxing dichloromethane (12 h).[8]

In order to ascertain the stereoselectivity in the pinacol cross-coupling reactions outlined in eq 1, we chose to begin with the aldehydes **1a** and **1b** where the geminal substituents are equivalent. As can be seen in Table I, both of

Scheme I



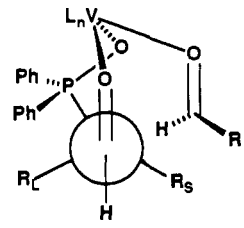


Figure 1.

these reactions provide high yields of the threo diols.[10] This high selectivity was anticipated based on other pinacol coupling reactions we have performed where the chelating aldehyde has had geminal substituents α to the formyl group.[5a,c]

Unlike in our other pinacol cross-coupling reactions, slow addition of chelating aldehyde 1 to a solution of the vanadium(II) reagent, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (4) (generated in situ from $VCl_3(THF)_3$),[8] and the nonchelating aldehyde is not necessary. Normally, slow addition is required to suppress homocoupling of the chelation assisted substrate.[5] However, if we assume that 1 equiv of 1 can form a chelate with 4, cross-coupling is presumably favored because the less hindered, nonchelating aldehyde effectively competes with a second equivalent of the hindered aldehyde 1 for coordination to the same metal center. In general, these cross-coupling reactions are approximately 50–70% complete after 2 h. However, yields are optimized when reaction times of 1–2 days are employed.[11] Noteworthy is the fact that homocoupling of 1 becomes competitive with cross-coupling when a hindered nonchelating aldehyde like pivaldehyde is employed (entry 7, Table I).

Having established that these reactions produce threo diols exclusively, we focused on the question of diastereofacial selectivity using substrates **1c–h**. As can be seen in Table I, excellent selectivity is observed in all cases, even when the difference between substituents was simply methyl versus ethyl.[12,13] Good selectivity is also observed in the case where two nonmethyl substituents are compared (entry 10, Table I). The sense of selectivity is predictable from a chelation-control model where the nonchelating aldehyde binds and reacts with the least hindered face of the chelating aldehyde (Figure 1).[5a,c,14,15]

(1) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Harmat, N. J. S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 2743.

(2) (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1990; Vol. 7, Chapter 3.2. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(3) An alternative approach involves stereospecific carbometalation of terminal alkynes. For examples, see: (a) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(4) For example, many of the cembranes and cembranolides possess this subunit. Tius, M. *Chem. Rev.* **1988**, *88*, 719.

(5) (a) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 4506. (b) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177. (c) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014.

(6) Buss, A. C.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2307.

(7) Teulade, M.; Savignac, P. *Synth. Commun.* **1987**, *17*, 125.

(8) See supplementary material for a general experimental and further details. For the in situ preparation of 4, see ref 5b or Raw, A. S.; Pedersen, S. F. *J. Org. Chem.*, in press.

(9) Compound 6 was prepared by chlorination of $Ph_2P(O)CH_2OH$ (Marmor, R. S.; Seyferth, D. *J. Org. Chem.* **1969**, *34*, 748) using PCl_5/$CaCO_3$ (Carman, R. M.; Shaw, I. M. *Aust. J. Chem.* **1976**, *29*, 133).

(10) The threo stereochemistry was confirmed by X-ray structural analysis of diol **2f**.

(11) Stereoselectivity does not change with time; even after a completed reaction was refluxed for 12 h.

(12) In one case, the relative stereochemistry indicated in equation 1 was established by X-ray structural analysis of diol **2f** (ref 10). In all other cases it was either assumed by analogy, or inferred from the stereochemistry of the allylic alcohols (3) prepared from 2. Stereochemistry of the allylic alcohols was established by NOE experiments and is consistent with the expected syn elimination from diol 2 (see ref 16).

Table I. Synthesis of Diols (2) and Allylic Alcohols (3) (See eq 1)[a]

entry	phosphinoyl aldehydes (1) no.	R^1	R^2	diols (2) R^3	no.	ds ratio[b,c,d]	yield (%)[e]	allylic alcohols yield (%)[f]
1	**1a**	CH_3	CH_3	*i*-Pr	**2a**	–[g]	84	84[h]
2	**1b**		$-(CH_2)_5-$	C_6H_{11}	**2b**	–[g]	87	93
3	**1c**	CH_3	Et	$PhCH_2CH_2$	**2c**	14:1	82	92
4	**1d**	CH_3	$(CH_3)_2C{=}CHCH_2$	*i*-Pr	**2d**	14:1	85	90[h]
5	**1e**	CH_3	Bn	CH_3	**2e**	28:1	94[i]	95[h]
6	**1e**	CH_3	Bn	$PhCH_2CH_2$	**2f**	43:1	89	94
7	**1e**	CH_3	Bn	*t*-Bu	**2g**	≥45:1	32[j]	98
8	**1f**	CH_3	*i*-Pr	*i*-Bu	**2h**	>99:1	94	91
9	**1g**	CH_3	Ph	$PhCH_2CH_2$	**2i**	–[k]	80	77
10	**1h**	Et	*i*-Pr	*n*-Pr	**2j**	7.5:1	81	91[h]

[a] For a representative experimental for the synthesis of **2** and **3** see the supplementary material. [b] The term ds refers to the diastereofacial selectivity for these reactions. Only threo diols were obtained. [c] Determined by ^{31}P NMR spectroscopy of the crude product mixture. Accuracy of the analysis by ^{31}P NMR spectroscopy was established by demonstrating that the *E*/*Z* ratio of allylic alcohols **3d,e,j** (by ^1H NMR of the crude product mixture), prepared from crude diols **2d,e,j**, was the same as the reported ds. [d] After purification of the diol by either flash chromatography (fc) or recrystallization (r), ds generally improved significantly: e.g. **2c**, 59:1 (r); **2d**, >99:1 (r); **2e**, 34:1 (fc); **2f**, 57:1 (fc); **2g**, >99:1 (fc); **2i**, >99:1 (r); **2j**, >99:1 (fc). [e] Isolated yield (%). [f] Unless otherwise noted, yields for **3** are based on elimination from purified diol **2**. The *E*/*Z* ratio of products was always equal to the ds of the purified or crude diol **2**. [g] Only the threo diol was obtained. [h] Crude **2** was used. Therefore, the yield is based on starting aldehyde **1**. [i] 1.1 equiv of acetaldehyde were used. [j] 41% of starting material (**1e**) was recovered. Approximately 20% of homocoupled products from **1e** was observed by ^{31}P NMR spectroscopy. [k] Not determined due to the presence of several other minor resonances in the ^{31}P NMR spectrum of the crude product mixture.

With high diastereofacial selectivity in hand all that remained to complete the proposed synthesis of allylic alcohols shown in eq 1 was to perform the Horner–Wittig elimination reaction.[16] This was accomplished using an excess of sodium hydride (4 equiv) in refluxing tetrahydrofuran (ca. 20–60 min).[8] Yields of the allylic alcohols were always high, and the elimination can be performed on the crude diols (**2**) (Table I). Alternatively, purification of the diols either by recrystallization or chromatography generally results in significant or complete enrichment of the major isomer (see Table I).

In summary, we have developed an efficient and stereospecific synthesis of 3,3-disubstituted allylic alcohols that employs the chelation assisted pinacol cross-coupling reaction as a key step. Extension of this chemistry to asymmetric syntheses of this class of alcohols is clearly feasible by beginning with enantiomerically pure chelating aldehydes. The high diastereofacial selectivity observed in these reactions also warrants further study. In particular, if the conformational properties of chelated **1** are responsible for this selectivity, then other chelation-controlled addition reactions to these aldehydes should be possible.[17] Such reactions could lead to a general and stereospecific synthesis of trisubstituted alkenes.

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735), the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735), Eli Lilly and Company, the Exxon Education Foundation, Monsanto Company, Rohm and Haas Company, and Syntex for financial support.

Supplementary Material Available: Representative procedures for syntheses of aldehydes **1**, diols **2**, and allylic alcohols **3** and ^1H and ^{13}C NMR, mass spectra, and elemental analyses data for all compounds (11 pages). Ordering information is given on any current masthead page.

(13) To our knowledge, diastereofacial selective additions of this magnitude, to a prochiral carbonyl bearing three non-hydrogen α-substituents, two of which are methyl and ethyl, is without precedent. For examples of chelation-controlled addition reactions to α-hydroxy(or alkoxy) carbonyls bearing two different non-hydrogen substituents, see: (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (c) Cram, D. J.; Allinger, J. *Ibid.* **1954**, *76*, 4516. (d) Cram, D. J.; Elhafez, F. A. A. *Ibid.* **1952**, *74*, 5828. For an additional example related to this area see: Reetz, M. T. *Nach. Chem. Tech. Lab.* **1981**, *29*, 165.

(14) For reviews of chelation-controlled addition reactions, see: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(15) The term "chelation-control" is used to identify a predictive model for the stereochemical outcome of these reactions (Figure 1). This model is not meant to suggest what the reactive intermediates are in these reactions.

(16) Buss, A. D.; Greeves, N.; Mason, R.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **1985**, 2307.

(17) Recently, Warren and co-workers have achieved high stereochemical control in the reduction of α-diphenylphosphinoyl ketones (i.e. $Ph_2P(O)CHRC(O)R'$ using sodium borohydride in the presence of cerium chloride. Elliott, J.; Hall, D.; Warren, S. *Tetrahedron Lett.* **1989**, *30*, 601.

Stereoselective Alkylations of Chiral, Phosphorus-Stabilized Benzylic Carbanions

Scott E. Denmark* and Roberta L. Dorow

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Summary: A series of 6-substituted 2-benzyl-3-*tert*-butyl-1,3,2-oxazaphosphorinanes was prepared in racemic and enantiomerically pure form. The diastereoselectivity of alkylation of the derived anions was examined as a function of ring substitution pattern, base, solvent, electrophile, and enantiomeric composition.

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