

UNUSUAL REACTION OF 2-TRIMETHYLSILYLETHYLIDENETRIARYLPHOSPHORANES
 (SEYFERTH-WITTIG REAGENT) WITH α -METHYLALDEHYDES: A NOVEL METHOD FOR
 HIGHLY CRAM-DIASTEREOSELECTIVE ADDITION OF VINYL ANION EQUIVALENT

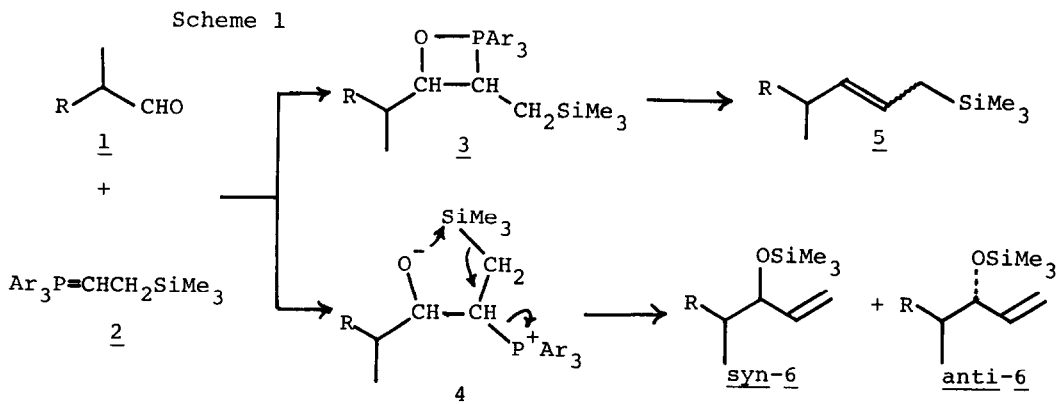
Masamitsu Tsukamoto, Hideo Iio, and Takashi Tokoroyama*

Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Summary: By the reaction of α -methylaldehydes with trimethylsilylethylidene-triarylyphosphoranes the introduction of vinyl group is effected in highly Cram-selective manner.

The Cram-diastereoselection, observed in the addition of a nucleophile to a carbonyl compound having the chiral center at the adjacent position, is the prototype of acyclic stereocontrol, while the degree of the selectivity is not generally high except the chelation control is operative.¹⁻³ We report in this communication a novel approach for highly Cram-selective addition of vinyl anion equivalent to α -methylaldehydes which make use of 2-trimethylsilylethylidene-triarylyphosphoranes.

In the reaction⁴ of 2-phenylpropanal (1, R = Ph) with 2-trimethylsilylethylidene-triphenylphosphorane (2, Ar = Ph),⁵ we observed the formation of the corresponding allylsilane 5 (R = Ph) was accompanied by the production of a byproduct 6 (R = Ph) in a larger amount ($6/5 = 0.8$), which would arise via betaine 4 or corresponding pentacoordinate silicon species⁶ by the eliminative 1,4-(C=O)-silyl migration^{7,8} as shown in Scheme 1. More interestingly the



latter reaction was found to show a good *syn*(Cram)-diastereofacial selectivity. This finding led us to scrutinize the reaction and to develop the novel stereoselective methodology.

Firstly we noticed the formation ratio of 6/5 varied considerably with the change in the concentration of reaction solution. When it was diluted by five times from the reported recipe,⁵ 6 formed in an increased ratio (6/5 = 2).¹¹ In the solvents tested THF was most advantageous for the production of 6 (6/5: Et₂O, 0.2; DME, 0.5). In the Table 1 is illustrated some scope of the reaction which was conducted at the condition thus standardized. A substantial amount of the eliminative rearrangement product proved to be obtained even from the aldehyde lacking α -methyl substituent (entry 1). The presence of the α -substitution in the phosphorane reagent resulted in the exclusive formation of the Wittig product (entry 3). The tributylstannylphosphorane reagent also gives rise to the rearrangement product, but in lesser extent than the silyl counterpart (entry 4). Subsequently we investigated to promote the eliminative rearrangement relative to the Wittig reaction by the modification of the phenyl group in the phosphorane reagent. The introduction of electron-donating group in the phenyl substituents of the phosphorane would attenuate the electron-demanding situation of the phosphorous atom by deminishing P-O attraction and/or by stabilizing the betaine-like intermediate. The result of the experiments in this direction is shown in Table 1 (entry 5-8). The effect caused by the introduction of methoxy groups is conspicuous for the increase of the 6/5 ratio and the predominant formation of 6 (R = Ph) over 5 (R = Ph) by ten times is realized by the use of tris(4-methoxyphenyl)phosphorane reagent. Although exclusive formation of 6 was observed in the reaction with tris(2-methoxyphenyl)phosphorane, the yield in this case lowered markedly (\sim 20%) due to the insolubility of the reaction intermediate.

Table 1. The formation ratio of the eliminative rearrangement product 6 versus the Wittig product 5^a

entry	phosphorane reagent	<u>6/5</u> ^b	entry	phosphorane reagent	<u>6/5</u> ^b
1.	Ph ₃ P=CHCH ₂ SiMe ₃	1.1	5.	Ph, (4-MeOPh) ₂ P=CHCH ₂ SiMe ₃	4
2.	Ph ₃ P=CHCH ₂ SiMe ₃	2.0	6.	(4-MeOPh) ₃ P=CHCH ₂ SiMe ₃	10
3.	Ph ₃ P=CMeCH ₂ SiMe ₃	\sim 0	7.	(2-MeOPh) ₃ P=CHCH ₂ SiMe ₃	>100
4.	Ph ₃ P=CHCH ₂ SnBu ₃	0.6	8.	(2-MePh) ₃ P=CHCH ₂ SiMe ₃	0.3

a. The reaction was conducted in THF at - 78 °C with the reagent concentration of 0.108 mmol/ml. The substrate is 2-phenylpropanal in all runs except entry 1 where 3-phenylpropanal was used.

b. The ratios were determined from the yields isolated after preparative TLC (as the free allylic alcohols in the case of 6). Generally the combined yields of 70 - 80% were secured.

Next the diastereofacial selectivity in the formation of the silyl ether

6 was examined on a variety of substrates with the tris(4-methoxyphenyl)phosphorane reagent as displayed in the Table 2. The syn-diastereoselectivity more than 90% was attained except in the conversion of 2-methylpentanal (entry 4) and the efficiency of the method is obvious when compared with the selectivity in the reactions with vinylmagnesium bromide. The formation of the allylsilane 5 shows a tendency to increase in the reactions where the higher diastereoselectivity is realized (entries 3 and 5) but the extent would be still tolerable.

Typical procedure: A solution of BuLi in hexane (1.5M, 0.57 ml, 0.86 mmol) is added dropwise into a stirred suspension of tris(4-methoxyphenyl)-2-trimethylsilylethylphosphonium bromide (352 mg, 0.78 mmol) in THF (3 ml) at 0 °C under nitrogen and the stirring is continued at ambient temp for 30 min. Iodo-methyltrimethylsilane (156 mg, 0.78 mmol) dissolved in THF (2 ml) is added and the mixture was stirred at room temp for 1 h, then cooled by dry ice-acetone bath. The addition of BuLi solution (0.52 ml, 0.78 mmol) is followed and, after removal of the bath, the mixture is stirred for 30 min. To the reagent solution thus prepared and cooled to -78 °C is added a solution of 2-phenylpropanal (70 mg, 0.52 mmol) in THF (2 ml). The mixture is allowed to react for 30 min. The cooling bath is removed and the reaction is quenched by the addition of water. Extraction with ether, washing with brine and evaporation of the solvent give a mixture of 5 (R = Ph) and 6 (R = Ph) which is dissolved in ethanol and treated with a few drops of 1M HCl. The products obtained after usual workup are separated on silica gel plates to afford trimethyl(4-phenyl-2-penten-1-yl)silane (9 mg) and 4-phenyl-1-penten-3-ol (67 mg) as a mixture of diastereomers (15:1).

Table 2. The vinylation reactions of α -methylaldehydes with tris(4-methoxyphenyl)trimethylsilylethylidenephosphorane

entry	substrate	formation ratio ^a of <u>6</u> to <u>5</u>	diastereomeric ratio ^b of <u>6</u> (<u>syn/anti</u>)
1.	2-phenylpropanal	10 : 1	15 : 1 (3 : 1) ^d
2.	3-phenyl-2-methylpropanal	- ^c	9 : 1
3.	2-cyclohexylpropanal ¹²	4 : 1	>20 : 1
4.	2-methylpentanal ¹³	- ^c	2.7 : 1 (1.3 : 1) ^d
5.	6 β -methoxy-3 α ,5 β - cyclo-23-norchol-22-al ¹⁴	3.3 : 1	>20 : 1 (3.5 : 1) ^d

a. Ratios based on the isolated yields.

b. Determined from the ¹H NMR integration of sec-methyl signals. The description of >20:1 means the signals due to the minor isomer were not discernable.

c. The allylsilane 5 was not detectable in the product.

d. The ratios in parentheses denote the selectivity observed in the reactions with vinylmagnesium bromide in THF at 0 °C.

In conclusion the novel vinylation method described herein is significant in that it provides a mean for the highly Cram-selective addition of vinyl group to α -methylaldehydes which is not generally attainable by the organo-metallic reagents. In view of the utility of the vinyl function for the synthetic manipulation we believe our method will be capable of finding a wide application in the stereoselective syntheses of natural products.

References and Notes

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8. This side reaction is interesting also in connection with the subtle mechanism of the Wittig reaction.⁹ The formation of oxaphosphetane intermediate via an energetically favorable¹⁰ four centered transition state may be competed by that of 4 by way of an antiperiplanar alignment, which collapse to yield 6 by the O-Si interaction rather than O-P. The latter reaction would become incentive in the present case through the O-Si affinity and the steric effect of α -methyl group in the aldehyde. The possibility that the production of 6 passes through the oxaphosphetane, which could be in equilibrium with the bataine 4 at all is ruled out, since the product ratios (6/5) were independent of the reaction time (5 min and 240 min) at the temperature of - 78 °C, where the decomposition rate of the oxaphosphetane 3 to yield 5 would be very slow.
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11. This result may be better to count in the solvent effect since the reaction solution in the original procedure⁵ contained much amount of hexane derived from the BuLi solution (THF/hexane = 5:3).
12. In view of the reported anti-Cram prediction³ the syn-configuration of the major product was confirmed by a chemical correlation with syn-4-phenyl-1-penten-3-ol (hydrogenations of the former and the latter with Pd-C and Rh-Al₂O₃ respectively).
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