Regio- and Stereo-controlled Methylation of γ-Silylallyl Phosphates by π-Allylpalladium Methodology

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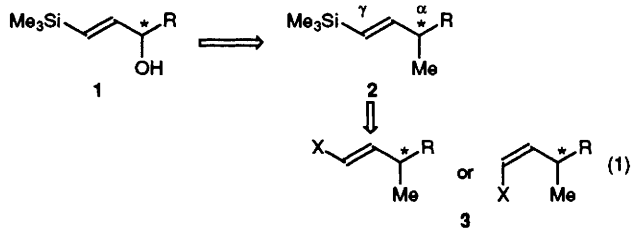
Palladium-catalysed methylation of diethyl phosphates derived from optically active γ-trimethylsilylallyl alcohols proceeds in a highly regio- and stereo-selective manner to give optically active vinylsilanes having an allylic methyl group.

Palladium-catalysed substitution of allyl esters with soft nucleophiles, such as active methylene compounds, is a well-documented, standard method for allylic alkylation and much data have been accumulated on its regio- and stereochemical aspects.[1] However, not much information has been reported on allylic alkylation with a Grignard reagent, a typical hard nucleophile,†[2] although some synthetic reactions involving alkylations of π-allylpalladium themselves have been reported.[3] Accordingly, copper,[4] nickel[5] and, most recently, iron[6] catalysts have been much more frequently used in this type of transformation[7] and the palladium methodology generally tends to be ignored. Herein we describe a palladium-catalysed alkylation of an allyl phosphate with a methyl Grignard reagent, in which the use of palladium is definitely advantageous.

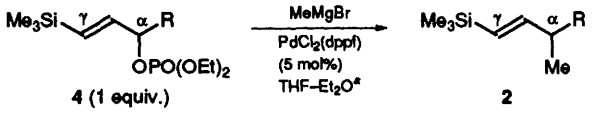
Highly optically active γ-trimethylsilylallyl alcohols **1**[8] are available by kinetic resolution in Sharpless asymmetric epoxidations[9] and have been used as starting materials for the synthesis of biologically active substances.[10] If the hydroxy groups are successfully transformed to α-methyl groups without loss of the enantiopurities, vinyl silanes **2** result with an optically active tertiary carbon centre bearing a methyl. [eqn. (1)]. Manipulation of the vinyl silane moiety of **2** as illustrated in eqn. (1) where X stands for H, alkyl, aryl, acyl, halogen, CN, Bu_3Sn, *etc.* based on well-precedented transformations[10,11] makes **2** a versatile chiral intermediate for the synthesis of terpenoids and other naturally occurring products.[12]



The crucial methylation step seemed, at first, straightforward by a two step sequence which consists of conversion of the hydroxy group of **1** to a leaving group and then reaction with a methylmetal in the presence of a transition metal catalyst mentioned above. A wide variety of combinations of the derivatives of **1** (phosphate, carboxylates and methanesulfonate) and organocopper reagents including MeCu, MeM/CuX cat., MeCu(CN)M, Me_2CuM and MeCu(Th)(CN)M_2 (M = Li or MgBr, Th = 2-thienyl)[4] showed mostly γ-preferences in the methylation. A reaction of the methanesulfonate

† Palladium-catalysed substitution of allylic derivatives with a Grignard reagent is quite rare. This is partly due to a bias that side reactions, *e.g.*, ester hydrolysis, reduction *via* β-hydride transfer and homo-coupling, make this transformation complicated.

Table 1 Alkylation of **4** with MeMgBr

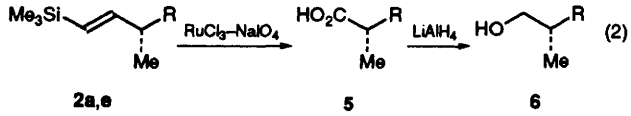


	4					2		
Entry	R	E.e. (Config.)	MeMgBr/ equiv.	*T*/°C	*t*/h	α/γ[b]	Yield (%)[c]	E.e. (%) (Config.)[d]
1	C_5H_{11} **a**		1.5	−20	15	(98:2)	(89)	
2	**a**	>99% (*R*)	3	−20	36	97:3(99:1)	69(91)	98 (*S*)
3	**a**		,,	0	16	(98:2)	(100)	
4	C_8H_{17} **b**		,,	−20	17	97:3	78	
5	$(CH_2)_4OTBS$ **c**		,,	−20	18	98:2	77	
6	$CH_2CH{=}CHC_5H_{11}$-*cis* **d**		,,	0	17	95:5	82	
7	CH_2CHMe_2 **e**	>99% (*R*)	,,	0	12	96:4(97:3)	60(81)	97 (*S*)
8	$CH_2C(=CH_2)CH_2OTBS$ **f**		3.6	−10	48	97:3	60(87)[e]	
9	Cyclo-C_6H_{11} **g**		3	Room temp.	6	71:29(75:25)	66(77)	

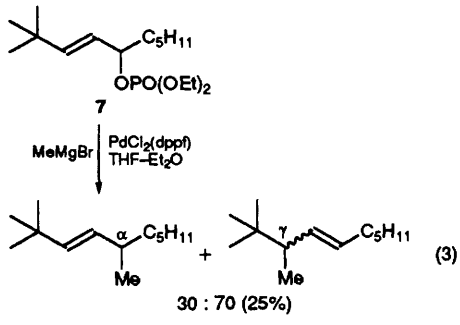
[a] Et_2O came from the Grignard reagent. [b] Determined by ^1H NMR of a crude or an isolated sample. When an isolated product was analysed, there was no evidence that regioisomers had been separated during isolation. Ratio determined by GLC analysis of a crude sample is shown in parentheses. [c] Isolated, combined yield of the regioisomers. Yield determined by ^1H NMR in parentheses. [d] See text. [e] Methylation to the TBS (Bu^tMe_2Si) ether moiety was only a trace if any.

of **1** [(R = C_5H_{11}, >99% e.e.) (enantiomeric excess)] and Me_2CuLi afforded the highest α:γ ratio of 78:22, but the optical purity of the α-product was disappointingly low (9% e.e.). The use of nickel catalysts [$NiCl_2(PPh_3)_2$, $NiCl_2$(dppp)‡ or Ni(acac)$_2$‡][5] together with MeMgBr or MeZnCl did not improve this reaction (α:γ ratio of 76:24). The most recently introduced Fe-catalysed alkylation of the diethyl phosphate of **1** (R = C_5H_{11}, >99% e.e.) [MeMgBr and 5 mol% Fe(acac)$_3$][6] achieved an almost complete regiochemical control (α:γ > 99:1), but the enantiopurity of the product did not exceed 93% even under carefully optimized conditions. However, we finally found that exposure of the diethyl phosphates of **1** to methylmagnesium bromide and $PdCl_2$(dppf)‡[2] (5 mol%) led to a very clean reaction to give highly optically active vinylsilanes **2** having the methyl group at their allylic position. The results are summarized in Table 1.§

Of the alcohol derivatives involving phosphates, carboxylates and silyl ether, diethyl phosphate **4** was marginally best, because it is readily prepared from **1** [BuLi, $(EtO)_2POCl$, 72–93% yield][13] and acts as a reactive leaving group, but is still resistant to P–O bond cleavage by the Grignard reagent. Other Pd catalysts, $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$, showed less satisfactory regioselectivities. The number of equivalents of MeMgBr (which we usually added in excess to ensure a complete reaction) and the reaction temperature did not affect the regioselectivity (entries 1–3). γ-Trimethylsilylallyl phosphates **4** having various primary alkyl chains (R in Table 1) showed regioselectivites of 95:5–99:1 with the olefin geometry being exclusively *trans* (>99:1) (entries 1–8), but substitution with a cyclohexyl group showed only a modest α-selectivity (entry 9). As shown in Table 1, the stereoselectivity has been verified to be excellent in a couple of representative cases (entries 2 and 7): virtually complete, overall inversion of configuration[14] at the alcoholic carbon of the starting ester has been established by ^1H NMR chiral shift study [Ag(fod)-Eu(hfc)$_3$[15]] of the vinylsilane **2** as well as by the MTPA‡ method[16] after derivatization to the known, optically active alcohol **6** [eqn. (2)].[17] The observed inversion of configuration is consistent with the stereochemical outcome found for the π-allyl palladium formation (inversion) and its reaction with a hard nucleophile (retention).[1d,14]



The sterically demanding Me_3Si group at the γ position was most likely to account for this excellent α-regioselectivity[18,19] as evidenced by the fact that increasing the size of the R group in another allylic terminus decreased the regioselectivity (*cf.* entries 1–8 and entry 9). However, this interpretation is so superficial that a *tert*-butyl analogue (**7**) of **4** gave a mixture of several products in which the α-methylated product was surprisingly a minor constitutent under the similar reaction conditions [(eqn. (3)]!. Thus, the electronic effect of the silyl group should also be responsible for the clean methylation.



‡ *Abbreviations used*: dppp: 1,3-bis(diphenylphosphino)propane; Hacac: pentane-2,4-dione; dppf: 1,1′-bis(diphenylphosphino)ferrocene; MTPA: α-methoxy-α-(trifluoromethyl)phenylacetic acid.

§ *Typical procedure*: To a stirred solution of **4a** (*R*, >99% e.e., 20 mg, 0.0595 mmol) in tetrahydrofuran (THF) (0.6 ml) under nitrogen was added $PdCl_2$(dppf) (2.2 mg, 0.003 mmol). The mixture was cooled to −78 °C and MeMgBr [3.0 mol dm^{-3} in diethyl ether (Aldrich) 0.060 ml, 0.179 mmol] was added dropwise. (Note: Adjustment of the solvent composition to *ca.* 10:1-THF/ether is strongly recommended to get a reproducible result). After stirring for 30 min at the same temperature, the resultant mixture was warmed to −20 °C and was stirred for an additional 7 h. Then NH_4Cl (sat.) was added and the mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue, ^1H NMR analysis of which had revealed the presence of the desired methylated compound in 91% yield, was chromatographed on silica gel with hexane to afford **2a** (*S*, 98% e.e., 8.1 mg, 69%) as an oil. See text for isomeric ratio and e.e.

The highly selective methylation of the allyl phosphate with Grignard reagent is a new route to a series of allylic alkylations catalysed by palladium and is synthetically useful to provide versatile building blocks having a chiral tertiary alkyl centre.

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References

1 Reviews: (*a*) B. M. Trost, *Tetrahedron*, 1977, **33**, 2615; (*b*) *Acc. Chem. Res.*, 1980, **13**, 385; (*c*) J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer Verlag, Berlin, 1980; (*d*) B. M. Trost and T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon Press, Oxford, 1982, vol. 8, p. 799; (*e*) J. Tsuji, *Tetrahedron*, 1986, **42**, 4361; (*f*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1988, **28**, 1173; (*g*) C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089.

2 Phenylation has been reported: T. Hayashi, M. Konishi, K.-I. Yokota and M. Kumada, *J. Organomet. Chem.*, 1985, **285**, 359.

3 Methyl Grignard reagent: Y. Castanet and F. Petit, *Tetrahedron Lett.*, 1979, 3221; allyl Grignard reagent: A. Goliaszewski and J. Schwartz, *J. Am. Chem. Soc.*, 1984, **106**, 5028; T. Hayashi, M. Konishi and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 1984, 107.

4 G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York, 1980; B. H. Lipshutz and S. Sengupta, *Org. React. (N.Y.)*, 1992, **41**, 135; B. H. Lipshutz, *Synthesis*, 1987, 325.

5 H. Felkin and G. Swierczewski, *Tetrahedron*, 1975, **31**, 2735; P. W. Jolly, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon Press, Oxford, 1982, vol. 8, p. 713.

6 A. Yanagisawa, N. Nomura and H. Yamamoto, *Synlett*, 1991, 513.

7 Review: R. M. Magid, *Tetrahedron*, 1980, **36**, 1901.

8 Both enantiomers of **1** are readily available, see Y. Kitano, T. Matsumoto and F. Sato, *Tetrahedron*, 1988, **44**, 4073.

9 Reviews: M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1985, vol. 5, p. 247; A. Pfenninger, *Synthesis*, 1986, 89; R. A. Jonson and K. B. Sharpless, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 7, ch. 3-2.

10 Review: F. Sato and Y. Kobayashi, *Synlett*, 1992, 849.

11 E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, 1981, W. P. Weber, *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983.

12 J. S. Glasby, *Encyclopaedia of the Terpenoids*, Wiley, Chichester, 1982.

13 A. Yanagisawas, N. Nomura, Y. Noritake and H. Yamamoto, *Synthesis*, 1991, 1130.

14 G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257.

15 T. J. Wenzel and R. E. Sievers, *J. Am. Chem. Soc.*, 1982, **104**, 382.

16 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.

17 For the preparation of authentic **5**, see D. A. Evans and J. M. Takacs, *Tetrahedron Lett.*, 1980, 4233.

18 For Pd-catalysed allylic alkylation with active methylene compounds in trimethylsilylallyl systems, see T. Hirao, J. Enda, Y. Ohshiro and T. Agawa, *Tetrahedron Lett.*, 1981, **22**, 3079; B. M. Trost and C. R. Self, *J. Am. Chem. Soc.*, 1983, **105**, 5942; J. Tsuji, M. Yuhara, M. Minato, H. Yamada, F. Sato and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 343.

19 H. Inami, T. Ito, H. Urabe and F. Sato, *Tetrahedron Lett.*, 1993, **34**, 5919.