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Unusual Reactivity of Acetate *versus* Carbonate in Palladium-Catalyzed Nucleophilic Substitutions : A Strong Silicon Effect.

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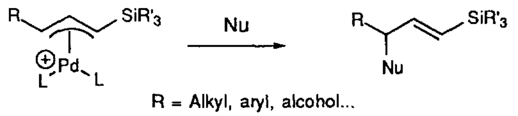
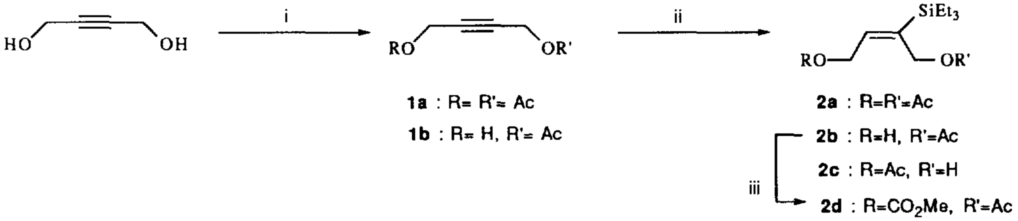
Abstract : The presence of a silicon group reverses the relative reactivity of carbonate and acetate in palladium-catalyzed nucleophilic substitutions. Copyright © 1996 Published by Elsevier Science Ltd

π-allyl palladium chemistry with silicon substituted electrophiles has been well studied since the pionners' work of Hirao.[1] Electrophiles such as allyl acetates, epoxides and carbonates are good leaving groups and allow the introduction of carbon[2] or nitrogen nucleophiles.[3] Attack of the nucleophile on the complex is directed by the substituent and usually[4] gives vinyl silanes (scheme 1).



Scheme 1

Surprisingly to our knowledge, in palladium-catalyzed nucleophile substitution, there is only one example where silicon is at the central position of the π-allyl cationic palladium complex.[5] During the course of our study on palladium-catalyzed cyclization of vinyl epoxide[6] we had the opportunity to look for the reactivity of such allylic substrates. In this letter, we present the reactivity of different allylic acetates relative to their position to the silicon substituent. In addition, accessible difunctionalized allylic compounds in which the two leaving groups are differentiated only by the silicon position have been chosen for this purpose (scheme 2). The reactivity in palladium chemistry of this type of dielectrophile is well documented,[7] moreover they could serve to build more elaborated molecules.[8]

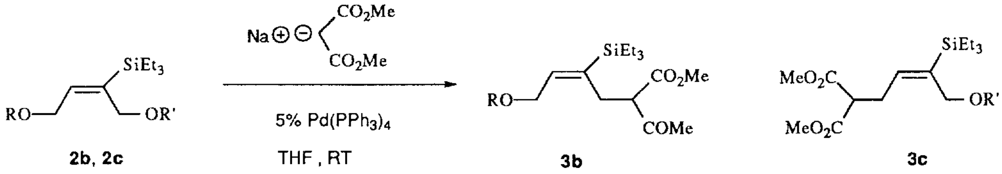


i) NaH 0.3 eq., Ac_2O, 0.3 eq. for **1b** or Ac_2O, Pyridine for **1a** ii) $HSiEt_3$, $H_2PtCl_6{,}6H_2O$ cat. iii) $ClCO_2Me$, Pyridine

Scheme 2

The starting molecules were prepared from 2-butyne-1,4-diol by acetylation of one or both alcohols using standard procedures. The mono- and diacetates alkynes **1a, 1b** were quantitatively converted to vinyl silanes by hydrosilylation with triethylsilane catalyzed by H_2PtCl_6, $6H_2O$.[9] The monoacetate **1b** gives a mixture of two regioisomers **2b** and **2c**, the corresponding ratio varying from 60/40 to 80/20 depending on the reaction temperature.[10] Attempt to increase the regioselectivity by the replacement of the methyl acetate by a trimethyl acetate group was unsuccessful.[11] Flash chromatography on silica gel allowed the isolation of pure compounds. For the present study, **2b** was also converted to the corresponding carbonate **2d** in quantitative yield with methyl chloroformate in the presence of pyridine.

In a first set of experiments, we compared the relative reactivity of **2b** and **2c** with sodium dimethylmalonate in the presence of catalytic tetrakis(triphenylphosphine)palladium (scheme 3).



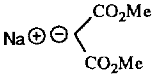
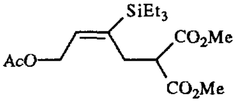
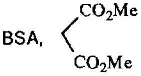
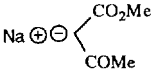
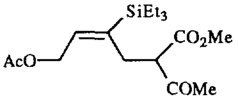
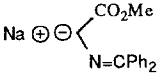
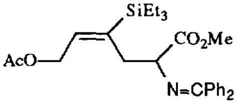
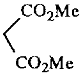
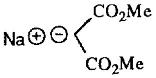
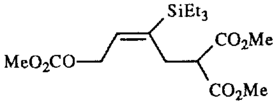
Scheme 3

These two molecules present only one leaving group allowing the totally regioselective introduction of nucleophiles. Compound **2b** reacts with dimethyl malonate to give after 1h at R.T. the expected substituted product **3b** (R = H) in 64 % yield. For **2c**, the same reaction proceeded in 10h at R.T. to furnish **3c** (R' = H) with a moderate yield of 40%. At this stage of the study it appears that β-acetates -relative to silicon- are better leaving groups than γ-acetates. To be useful in synthesis, the reactivity of the two leaving groups has to be quite different. In these conditions, a solution of **2b** and **2c** was mixed with half equimolar amount of sodiomalonate in the presence of $Pd(PPh_3)_4$. It has been observed in TLC and GC that **2b** reacted immediately with the nucleophile whereas **2c** did not participate. After malonate was consumed (1h, R.T.), **2c** was totally recovered and **2b** disappeared leading to the corresponding substituted product **3b**.

After this preliminary work, we have examined the reactivity of difunctionalized molecules where the two allylic potential leaving groups are discriminated by the silicon atom. First reactions were performed with (*E*)-1,4-diacetoxy-2-triethylsilyl but-2-ene **2a** with dimethyl malonate in the presence of 5 mol% of palladium catalyst (see table)[13]. In neutral or basic conditions, **2a** gives the corresponding adduct in 50 and 85 % yields respectively and with a total control of the regioselectivity (TLC, NMR and GC) (entries 1-2). In these reactions, PPh_3 and diphenylphosphinoethane (dppe) are both convenient ligands for palladium. As expected, silicon atom differentiates the two potential leaving groups : only the β-acetate relative to silicon is substituted, the other one in γ-position does not react.

We also tested the behavior of **2a** with two other stabilized carbonucleophiles. Methyl acetoacetate and methyl *N*-(diphenylmethylene)glycinate[12] react with the same efficiency in terms of yields and regioselectivity (entries 3-4). On the other hand, stereoselectivity decreases from malonate to imino ester due to an increase of the bulkyness of the nucleophile.

Table : Alkylation of difunctionalized substrates catalyzed by Pd(0).

Entry	Electrophile	Nucleophile	Conditions[a] t (h)	 T(°C)	Major product	Yield[c] (%)	E/Z ratio
1	**2a**	 $Na^{\oplus}\,{}^{\ominus}CH(CO_2Me)_2$	1	50		85	90/10
2	**2a**	 BSA, $CH_2(CO_2Me)_2$	1	50[b]	*idem*	50	85/15
3	**2a**	 $Na^{\oplus}\,{}^{\ominus}CH(CO_2Me)(COMe)$	4	RT		67	90/10
4	**2a**	 $Na^{\oplus}\,{}^{\ominus}CH(CO_2Me)(N{=}CPh_2)$	3	60		85	70/30
5	**2d**	 $CH_2(CO_2Me)_2$	12	50[b]	/	/	/
6	**2d**	 $Na^{\oplus}\,{}^{\ominus}CH(CO_2Me)_2$	0.5	50[b]		64	90/10

a) Catalyst prepared *in situ*, 5 mol% $Pd(PPh_3)_4$; b) 5 mol% $Pd(dppe)_2$; c) non optimized yields after purification

BSA : N,O-bis trimethylsilylacetamide

As it is known that carbonates are better leaving groups than acetates[14] and in order to control the regioselectivity of the attack -proximal *versus* distal relative to the silicon-, we checked the reactivity of the acetate-carbonate **2d** with malonate. In neutral conditions, no reaction was observed (entry 5). Surprisingly, in presence of the sodium salt of malonate, the substitution occured at the proximal position (entry 6). In fact, in this peculiar dielectrophile, the leaving group is not as we could have expected the carbonate but the acetate. Such selectivity confirms the strong directing effect of the silicon group which could be interpreted by electronic factors. On another hand, steric interactions with the palladium ligands may account for these results.

In summary, we have shown that the presence of the silicon group controls the regioselectivity of the palladium-catalyzed nucleophilic substitutions. Moreover, it reverses the relative reactivity of allylic acetates and carbonates. Work is under progress to determine which effect, electronic or steric, predominates to explain such inversion of reactivity between acetate and carbonate.

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13. All new compounds have been fully characterized. Typical procedure for alkylation :
    The materials were dried by flame before reaction and kept under Argon. Pure dimethyl malonate (1.2 mL, 10.5 mmol) was added to a cold suspension of NaH (60 % in mineral oil, 420 mg, 1 eq) in THF (20 mL). After 30 min., a preformed solution of $Pd(OAc)_2$ (3 mol %), PPh_3 (12 mol %) and *(E)*-1,4-diacetoxy-2-triethylsilyl-but-2-ene **2a** (3 g, 1 eq) in THF (4 mL) was added. The mixture was warmed to 50 °C and evolution followed by TLC. After 1h, a satured solution of aqueous NH_4Cl (50 mL) was added. The solution was extracted with ether (2x50 mL), the organic layer washed with brine (2x50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by chromatography [R_f=0.5 (PE:EE 7:3)] or distillation [Eb = 130°C (10^{-2}mm)] yielded to 3.20 g (85%).
    Anal. calcd. for $C_{17}H_{30}O_6Si$: C, 56.95 ; H, 8.43. Found : C, 56.93 ; H, 8.46.
    ^1H NMR (400 MHz, $CDCl_3$) : δ : 5.85 (t, J = 6 Hz, 1H) ; 4.71 (d, J = 6 Hz, 2H) ; 3.75 (s, 6H) ; 3.43 (t, J = 8 Hz, 1H) ; 2.77 (d, J = 8 Hz, 2H) ; 2.10 (s, 3H) ; 0.90 (t, J = 8 Hz, 9H) ; 0.60 (q, J = 8 Hz, 6H).
    ^{13}C NMR (50 MHz, $CDCl_3$) δ : 170.8, 169.2, 138.5, 138.0, 61.3, 52.6, 51.4, 29.6, 21.0, 7.2, 3.1.
    IR (neat) 2940, 2900, 2870, 1740, 1610, 1450, 1220, 1150, 730 cm^{-1}.
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