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Silicon-based Formation of Carbon-Carbon Bonds

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The image shows the cover of PharmaChem magazine, tilted at an angle. The main headline on the cover is "FARNABIOS[®] at the heart of healthcare". Below this, there is an illustration of two fishbowls; a small goldfish is jumping out of the water in the smaller bowl on the left, towards the larger bowl on the right. The text "A further leap to offer an additional product line: a brand **NEW HPAPI FACILITY**" is prominently displayed. Below this text is a row of seven colored boxes, each containing a product category: Oral Cephalosporins (green), Oral Hormones (light green), Highly Potent Substances (red), Oral Steroids (orange), Sterile Cephalosporins (dark blue), Sterile Steroid (light blue), and Antineoplastics (yellow). To the right of these boxes is a pink box labeled "Antineoplastics". At the bottom right, there is a logo for "health and safety are our concern" featuring a tree. The website "www.farnabios.net" is printed at the bottom. The magazine's masthead "PharmaChem" is at the top, with "ISSN 1720-4003" and "ANNO 9 - NUMERO 9/10 2010" in the top right corner. At the very bottom of the page, outside the magazine cover, it says "published by B5 srl Via Cesare da Sesto, 10 • 20123 Milano (Italy)".

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Silicon-based formation of carbon-carbon bonds

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INTRODUCTION

HATANAKA and HIYAMA first reported the palladium-catalyzed, fluoride-promoted reaction of aryl, alkenyl, allyl, and ethynyl-trimethylsilanes with aryl, vinyl and allyl halides to form the respective cross-coupled products (1). Since that time many variations of the transition metal-catalyzed cross-coupling of organosilanes with organic halides and related derivatives have been reported. Many of these require the use of fluoride ion promotion while others do not (2-5). The majority of these silicon-based carbon-carbon bond formation reactions have been applied to systems wherein the carbons from both partners are either sp^2 or sp carbons. The focus of this short review is on the application of organosilanes to the addition to aldehydes and ketones, their α,β -unsaturated cousins and to some selected sp^3 systems. In this regard they offer alternatives to the reactions of organomagnesium, organolithium, organocopper and other reagents.

1,2-ADDITION OF ORGANOSILANES TO ALDEHYDES AND KETONES

In an interesting differentiation of reactivity aryltrimethoxysilanes can show divergent pathways in their reaction with aldehydes. Thus, in the presence of fluoride ion addition to the carbonyl occurs in high yield (Eq. 1, Figure 1) providing a straightforward alternative from the more classical approaches to transformation. On the other hand, in the presence of the palladium phosphine acid catalyst, POPd, an oxidative esterification (Eq. 2) occurs (6).

Arylcarbinols are also produced in the reaction of the aryltriethoxysilane with aldehyde under the influence of sodium hydroxide, which works better than fluoride ion. Enones and related species react in a Michael fashion under these conditions (7).

The very stable and readily prepared and handled pentafluorophenyl-trimethylsilane reacts with aldehydes or ketones to form the pentafluorophenyl-

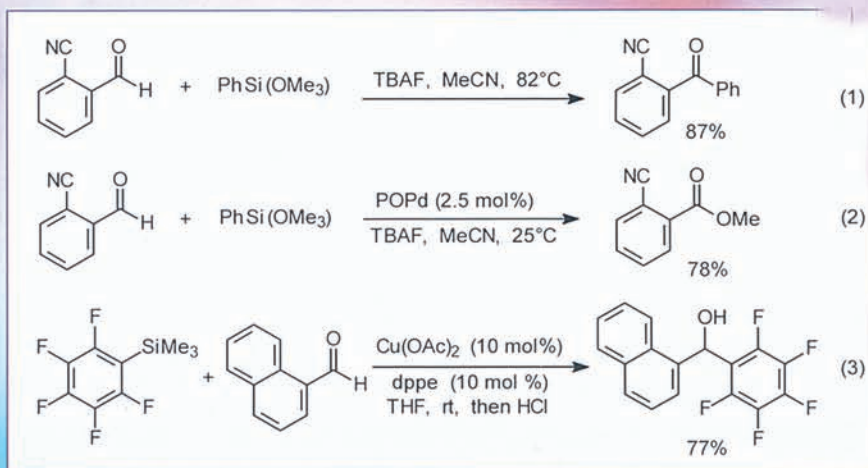


Figure 1

carbinol in good yields (8). This reaction can be promoted by cupric acetate, but requires a diphosphine ligand (Eq. 3).

A hetero-cyclocarbene copper fluoride complex works well for the conversion of allylsiloxanes to allylcopper intermediates, which then allylate aldehydes. Thus, the allylation of aldehydes with allylsiloxanes under the catalysis of

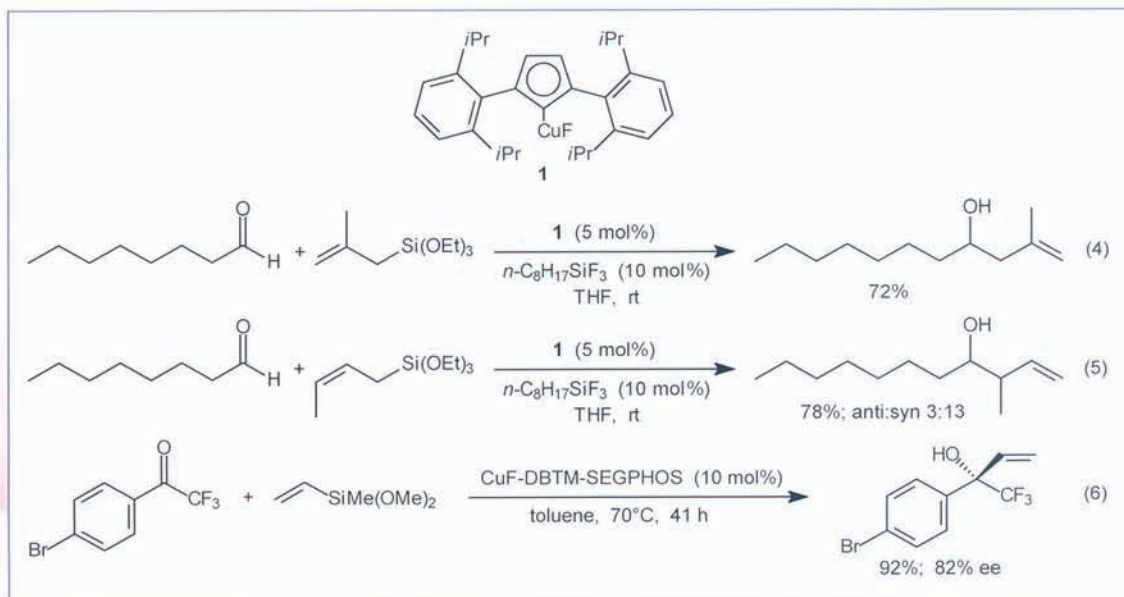


Figure 2

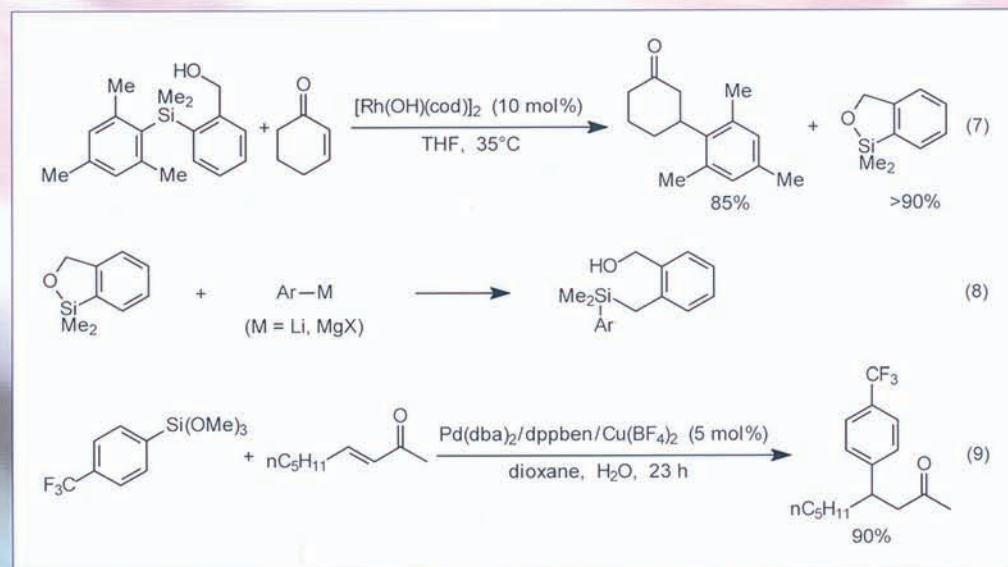


Figure 3

NHCCuF, **1**, results in good yields of the corresponding homoallylic alcohol (Eqs. 4, 5, Figure 2). The reaction is enhanced by the promotion of octyltrifluorosilane. (Z)-Crotyltrimethoxysilane shows only a modest selectivity towards the anti diastereomer (9).

Simple base catalysis can be used to form propargyl alcohols from the reaction of alkynyltrialkoxysilanes with aldehydes or ketones. The yields of the corresponding propargyl alcohols are modest to excellent. A similar result was obtained with the reaction with the *tert*-butylsulfinyl imine of benzaldehyde to form the corresponding propargylamine (10).

The asymmetric vinylation of trifluoromethyl-aryl ketones was carried out to give the trifluoromethyl-substituted allyl alcohols in good yields and modest

ee's (Eq. 6). This reaction does not work well with regular ketones showing the need for the activation of the carbonyl group by the trifluoromethyl group. Phenylethynyltriethoxysilane gave a 99% yield and 46% ee when reacted with phenyl(trifluoromethyl) ketone (11).

1,4-ADDITION OF ORGANOSILANES TO ALDEHYDES AND KETONES

A novel approach to the Michael arylation of enones with arylsilanes is via the use of the *o*-hydroxymethylphenyl ligand on silicon (Eq. 7, Figure 3). This ligand can form an intramolecular complex with the silyl group activating it for reaction (12). Moreover, the organosilane can be recycled (Eq. 8). This has been further

employed for the synthesis of allylsilanes from β -silylenones (13).

Michael arylation of enones and enals with aryltrimethoxysilanes in aqueous medium is possible (Eq. 9) (14). The Michael addition of arylsilanes to enones and enals is also catalyzed by palladium acetate, fluoride ion with antimony trichloride promotion (15).

Aryltrialkoxysilanes react with Baylis-Hillman acetate adducts, most likely through a π -allylpalladium intermediate, leads to a preponderance of the *Z* isomer of the resultant α -substituted α,β -unsaturated ester. The best solvent for the transformation was found to be a PEG ether (16).

ENANTIOSELECTIVE 1,4-ADDITION OF ORGANOSILANES TO ENONES

The asymmetric 1,4-arylation and vinylation of enones is possible with aryl- or vinylsilanes and rhodium catalysis in the presence of (S)-binap (Eqs. 10, 11, Figure 4). The yields are good and the ee's are better than 90%. The stereochemistry of the vinylsilanes is maintained with good selectivity in the product (17).

The asymmetric addition of aryltriethoxysilanes to cyclic enones, α,β -unsaturated lactones, and α,β -unsaturated lactams (Eq. 12) is a route to enantioenriched β -arylated

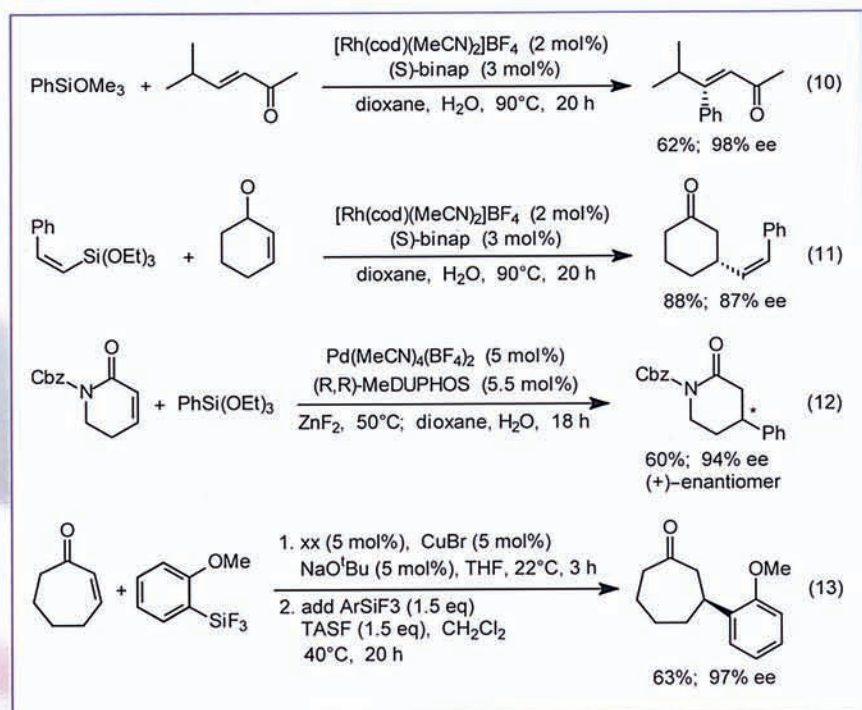


Figure 4

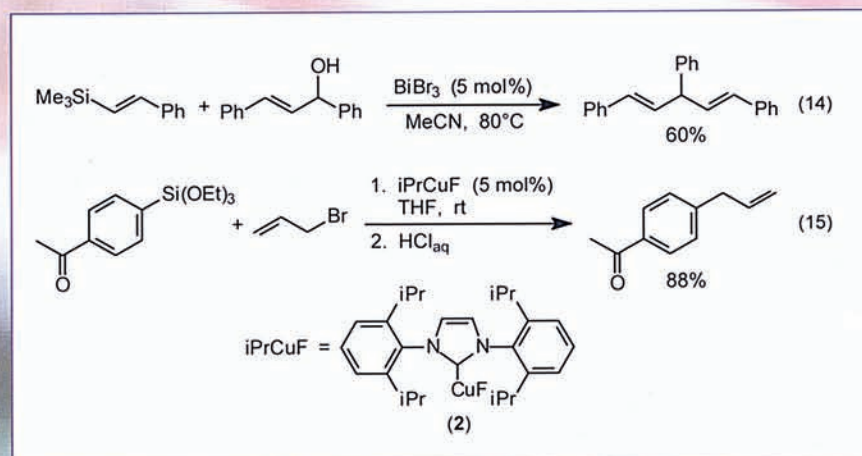


Figure 5

ketones, lactones and lactams. The yields are good and the ee's good to excellent with the exception of those for the lactones, which gave good ee's, but poor yields (18). The enantioselective addition of aryltrifluorosilanes to enones has also been reported (Eq. 13). Here again the yields and ee values are good, although the aryltrifluorosilanes are more difficult to prepare and typically come from the trialkoxysilanes (19).

A chiral carbene copper complex was used for the enantioselective addition of aryl- and vinyltrifluorosilanes to enones. The arylations occur in high yields and with high enantioselectivity

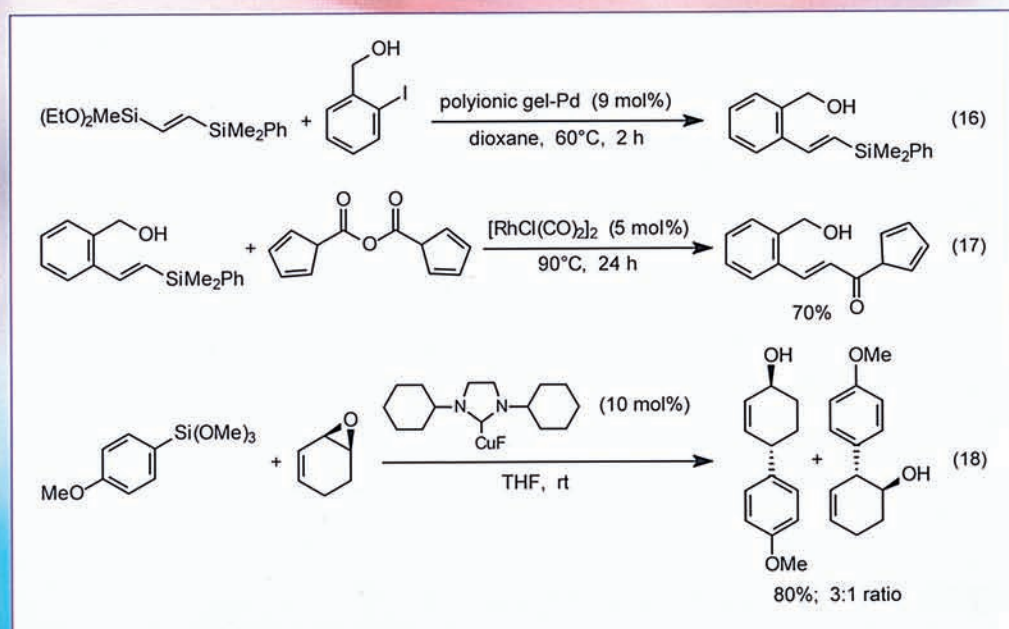


Figure 6

whereas the vinylations take place in high yields, but with only moderate ee's. Both reactions require the assistance of fluoride ion in the form of TASF (20).

The asymmetric alkylation of enones with alkynylsilanols has been shown to occur with high enantioselectivity under the promotion of chiral rhodium catalysts to yield 5-ketoalkynes in good yields and high ee's (21).

Excellent yields of the conjugate arylation of α,β -unsaturated aldehydes, ketones, esters, acrylonitriles and nitroalkenes can be carried out with aryltrimethoxysilanes in water when catalyzed by POPd1, a phosphinous acid palladium complex (22).

REACTION OF ORGANOSILANES WITH SOME OTHER SP^3 SYSTEMS

Various vinyltrimethylsilanes couple nicely with alcohols under the catalytic influence of indium trichloride or bismuth tribromide (Eq. 14, Figure 5). No great difference was found between the two catalysts with yields ranging from 26 to 97%. The stereochemistry of the vinylsilane is maintained in the product with the (E)-vinylsilanes being much more reactive and the (Z)-isomers giving very poor yields (23). Interestingly, even though the trimethylsilyl derivatives are used here fluoride promotion is not necessary for satisfactory reaction. In related work ethynylsilanes are coupled with propargyl alcohols to produce 1,4-dienes (24).

Organofunctional copper reagents are prepared in good yield via the reaction of a carbene copper (I) complex with arylsilanes. Allyltrimethoxysilane produces

the allylcopper reagent. The resulting copper reagents were trapped in high yields with allyl bromide (Eq. 15) (25). Other reactions of these readily available copper reagents should also be possible. A copper intermediate has been proposed in the allylation of *o*-trimethylsilylbenzyl alcohols with allyl chloride and *tert*-butoxycopper (I) (26).

A sequential combination of a Hiyama cross-coupling and a Narasaka acylation of vinylsilanes can be used to prepare (E)- β -aryl- α,β -unsaturated ketones (Eqs. 16, 17, Figure 6) (27). The yields of this two-step, one-pot sequence ranged from modest to good. A similar reaction is seen between aliphatic alkoxytrimethylsilanes and allyltrimethylsilanes to form three-carbon-extended olefins. In this case the reaction is promoted by indium chloride and iodine and the reaction is limited to the trimethylsilyl ethers of secondary and tertiary alcohols (28).

The direct arylation of alkyl bromides is possible via its coupling with an aryltrimethoxysilane. The reaction requires palladium (II) bromide and the hindered di-*tert*-butylmethylphosphine ligand as well as fluoride ion promotion to give good yields (29). Alkyl iodides work equally well. This has been extended to the nickel-catalyzed arylation of secondary halides in good yields (30). The nickel-catalyzed cross-coupling of unactivated alkyl halides with various organometallic reagents has been reviewed (31).

Aryltrialkoxysilanes have been shown to undergo a vinylogous addition to vinyl epoxides to generate 4-aryl allyl alcohols (Eq. 18) (32). This chemistry involves the transmetalation of the organosilane to an organocopper reagent, which then adds to the vinyl epoxide. The reaction also works for benzylic alkoxy silanes. Butadiene monoepoxide gives exclusively 1,4-addition, but a mixture of E and Z isomers with the E isomers predominating.

1-Trimethylsilylaryl acetylenes are coupled with propargyl chlorides to give allenynes in moderate yields (33). The reaction requires a fluoride ion source and is complicated by the formation of the homo-coupled diyne.

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