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GENERATION OF STANNYL DERIVATIVES OF METHYL KETONES VIA A SELECTIVE SILYL/STANNYL EXCHANGE AND ITS APPLICATION TO ALDOL REACTION

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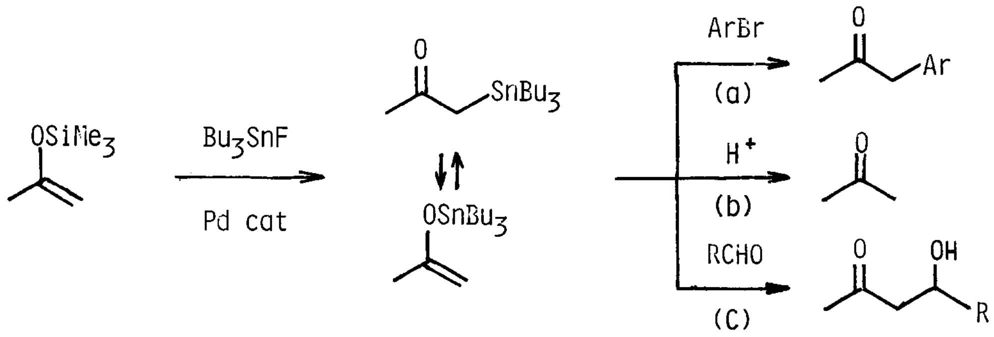
Summary: α-Stannyl derivatives of methyl ketones could be generated from the corresponding silyl enol ethers via a selective silyl/stannyl exchange and were used to prepare aldol products with almost complete regio- and chemo-selectivity.

α-Trialkylstannyl ketones and their tautomeric tin enolates are versatile enolate species and have attracted increasing attention in organic synthesis.[1] They are usually prepared by treating the corresponding enol acetates with trialkyltin alkoxides[2,3e] or by trapping metal enolates with a trialkyltin halide in situ.[2,3d] Since silyl enol ethers are readily available with a high regioselectivity by a variety of methods, a silyl/stannyl exchange reaction using silyl enol ethers as starting materials would provide another useful tool for generation of α-stannyl ketones (and/or tin enolates).

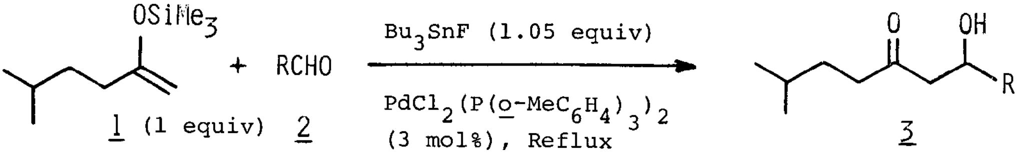
We previously described that α-stannyl ketones generated in situ from silyl enol ethers and tributyltin fluoride undergo arylation with aryl bromides in the presence of a palladium (Eq 1, a).[4] We also demonstrated the chemoselective desilylation of bis-silyl enol ethers by using Bu_3SnF and a palladium catalyst (Eq 1, b).[5] In this paper, we wish to report a further application of this silyl/stannyl exchange to a selective aldol reaction (Eq 1, c).



(1)

To attest the feasibility of the aldol reaction,[3] we have chosen the silyl enol ether of isoamyl methyl ketone 1 as the substrate and carried out the silyl/stannyl exchange reaction in the presence of aldehydes under the conditions summarized in the Table.[6,7]

Table. Aldol Reactions of 1 with Aldehydes.

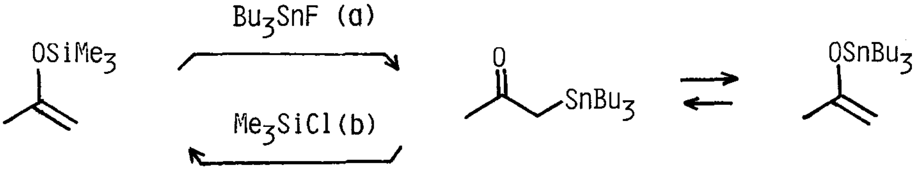


Run	R-CH=O (2)	Ratio (1/2)	Solvent	Period (h)	Yield (3,%)[a]
1	Benzaldehyde	1:1.1	THF	3	trace[b]
2	"	1:2	Benzene	7	36[b]
3	"	1:1.2	"	2	71 (20[c])
4	"	1.5:1	"	2	95[d]
5	Furfural	1:1.2	"	2	71
6	(E)-2-Hexenal	1:1.2	"	1	65
7	2-Ethylhexanal	1:1.1	"	1	59

[a] Isolated yield based on 1. [b] Reactions were attempted in the absence of the palladium catalyst. [c] Yield of the recovered parent ketone. [d] Yield based on 2.

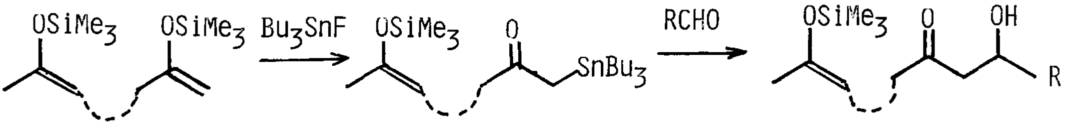
The reactions proceed in good yields with several types of aldehydes, but aromatic aldehydes serve as better acceptors than the others. The use of an excess amount of the silyl enol ether raises the product yield (run 4), because the enol ether may be partially consumed by protonation during the reaction. Careful analysis of the crude reaction mixture of 1 and benzaldehyde (run 3) by ^{1}H NMR revealed that the formation of the regioisomer, 4-hydroxy-3-isobutyl-4-phenyl-2-butanone, has not been observed within the limits of detection. Thus the regio-selectivity of the aldol reaction (hence that of the silyl/stannyl exchange reaction) is proved to be practically complete. The effect of the palladium catalyst in the present reaction is quite remarkable (cf. runs 2 and 3) and its exact role is under further investigation.

In contrast with the facile transmetalation reaction by the present system (Eq 2, path a), drastic conditions are usually required on using tributyltin methoxide as the stannylating reagent (e.g. at 180°C with continuous removal of methyl trimethylsilyl ether formed).[2] Moreover, it has been reported that formation of silyl enol ether is thermodynamically much favored in the reaction of stannyl derivatives with trimethylsilyl chloride (path b).[2]

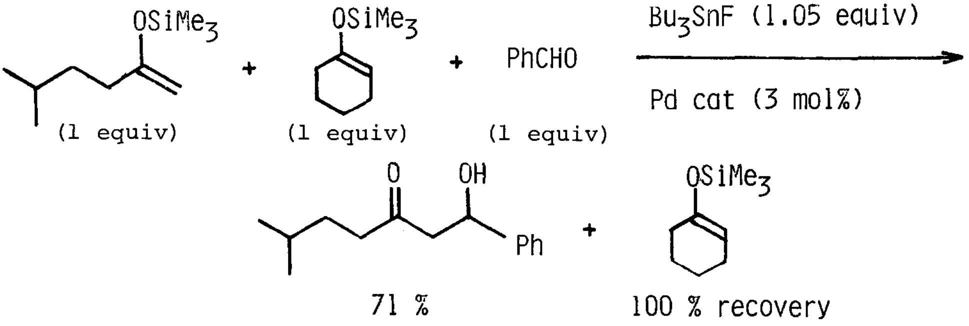


(2)

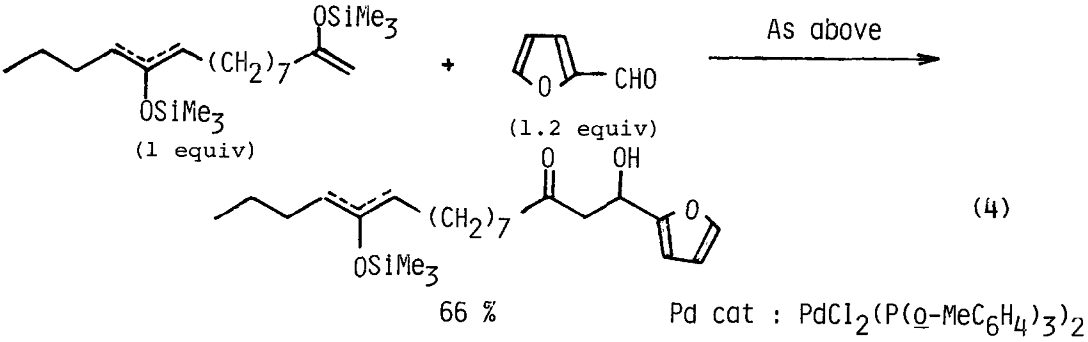
Noteworthy and of practical importance is that Bu_3SnF reacts selectively with a less hindered silyl enol ether moiety of bis-silyl enol ether to generate the silyl stannyl dienol ether, which undergoes the aldol reaction at the stannylated moiety as formulated below.



Equations 3 and 4 illustrate examples of such a selective aldol reaction, in which a new carbon-carbon bond formation took place on a methyl ketone site exclusively. The unaffected silyl enol ether function of the product would be useful for further synthetic elaborations.



(3)



(4)

Thus, the tin fluoride works as a hindered fluoride which has an ability to discriminate between more than two types of silyl enol ethers to generate the corresponding mono-stannylated species.

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6. A typical procedure is as follows (run 3 in the Table). The silyl enol ether of isoamyl methyl ketone (56 mg, 0.3 mmol), benzaldehyde (0.037 ml, 0.36 mmol), Bu_3SnF (97 mg, 0.315 mmol), and $PdCl_2(P(\underline{o}\text{-}MeC_6H_4)_3)_2$ (7 mg, 0.009 mmol) in benzene (0.8 ml) were heated at reflux for 2 hr under nitrogen. The resulting black solution was diluted with ether and treated briefly with 1 N NaOH under vigorous stirring. The aqueous layer was extracted with ether and the combined extracts were dried. Removal of the solvent followed by column chromatography on silica gel afforded the aldol, 1-hydroxy-6-methyl-1-phenyl-3-heptanone (47 mg, 71%).
7. Under the same conditions, 2-tributylstannyl-3-pentanone undergoes a similar aldol reaction in good yield.

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