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INTERMOLECULAR ALDOL REACTIONS VIA ALLYLIC O-STANNYL KETYLS

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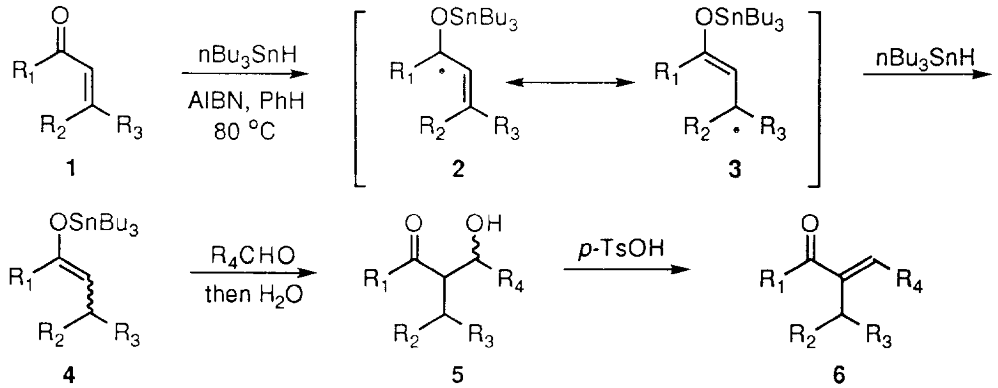
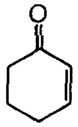
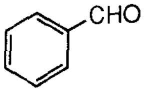
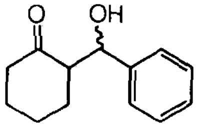
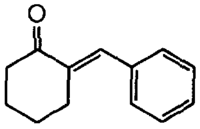
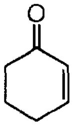
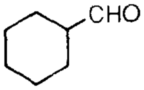
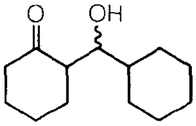
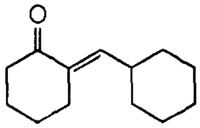
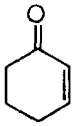
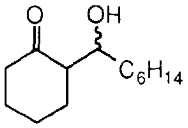
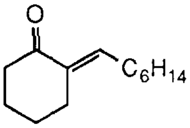
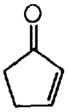
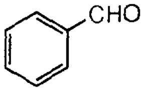
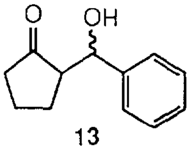
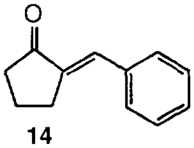
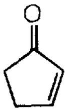
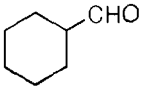
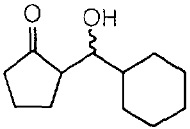
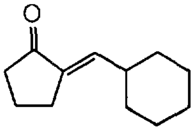
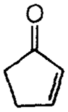
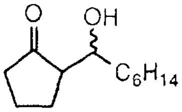
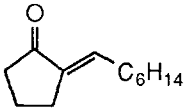
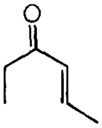
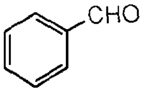
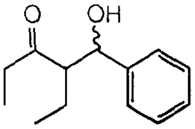
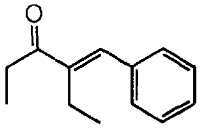
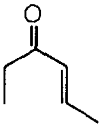
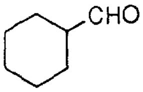
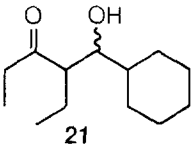
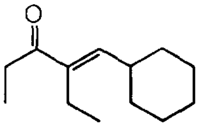
Abstract: A mild and neutral free radical reaction of an α,β-unsaturated ketone and tributyltin radical produced a resonance-stabilized allylic O-stannyl ketyl intermediate. A tin(IV) enolate, produced by subsequent hydrogen atom transfer, was next quenched with various aldehydes to yield an aldol product which was readily eliminated with *p*-toluenesulfonic acid to afford new α,β-unsaturated ketones with E/Z ratios up to >100:1.

Free radicals have been used in organic synthesis to construct a wide variety of carbon and heteroatom skeletons.[1] Allylic O-stannyl ketyls, obtained by the reaction of an α,β-unsaturated carbonyl group with tributytin hydride, can be a useful precursor to tin(IV) enolates.[2] The tin(IV) enolate represents a synthetic intermediate which utilizes and capitalizes on the nucleophilic character of the O-stannyl ketyl.[3-7] Although the nucleophilic properties of a ketyl are currently poorly understood, this radical oxyanionic species has great potential to become a synthetically useful tool.[7] The resonance stabilized allylic O-stannyl ketyl intermediate [**2** ↔ **3**] is readily afforded from $nBu_3Sn\bullet$ and α,β-unsaturated ketone **1** under standard free radical conditions. This subsequently leads to tin enolate **4** by hydrogen atom transfer from nBu_3SnH to the β-position of **3**, rather than the radical site in ketyl **2**. Upon quenching with an aldehyde, aldol product **5** is formed directly from the nucleophilic tin enolate in the same pot. This can be readily eliminated under acidic conditions to afford α,β-unsaturated ketone **6**.



This Letter describes the first examples of the process of intermolecular aldol reactions with α,β-unsaturated ketones and aldehydes promoted by tributyltin hydride.[7] The reaction provides a very mild and regioselective alternative to classical metal enolate formation but avoids strong bases such as LDA or reductive dissolving metal conditions. A related second regioselective process was also investigated herein which afforded a new β-hydroxy ketone through a second tin aldol reaction from the α,β-unsaturated ketone product of the first reaction.

Table. Aldol Reactions Via Allylic O-Stannyl Ketyls

Entry	Unsaturated Ketone	Aldehyde	Aldol	Yield (%) (Erythro:Threo)[14]	Dehydration Product	Yield (%) (E : Z)
1			 **7**	73 (6:1)	 **8**	92 (82:1)
2			 **9**	59 (6:1)	 **10**	95 (20:1)
3		Heptyl Aldehyde	 **11**	56 (4:1)	 **12**	89 (13:1)
4			 **13**	79 (1:1)	 **14**	78 (15:1)
5			 **15**	62 (3:1)[13]	 **16**	90 (>100:1)
6		Heptyl Aldehyde	 **17**	63 (1:1)	 **18**	94 (41:1)
7			 **19**	52 (2.5:1)	 **20**	53 (23:1)
8			 **21**	45 (4:1)	 **22**	88 (34:1)

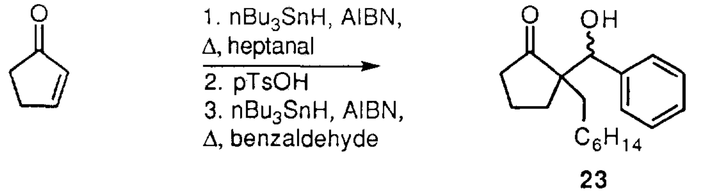
Several examples of the aldol sequence described above have been collected in the Table.[8-9,12] Yields were highest for the reaction of cyclic unsaturated ketones with benzaldehyde. Although the aldol products gave some modest ratios and yields, the corresponding acid dehydration products, yields and ratios were almost all very high. Only the dehydration producing **20** was special and required careful addition of small portions of acid. Too much *p*-TsOH in that case only decreased the yield and increased the amount of byproducts.

The aldol reaction was initially examined with the aldehyde present at the outset of the reaction. Compound **9** was successfully prepared in this manner, however, the yield was only 35%. The reduced nucleophilicity of the tin enolate prompted later attempts to generate the tin enolate prior to quenching it with the aldehyde at 80 °C, however, this gave **9** in 45% yield. With the aldehyde quench at 80°C, the erythro:threo ratio was determined to be 3.8:1. In an effort to improve the ratio, the enolate was quenched just above the freezing point of the benzene solvent at 10 °C. Not only did the erythro:threo ratio improve to 6:1 at this temperature, but also the yield improved to 59%. The identical reaction run in toluene allowed for quenching of the enolate at -78°C, but the erythro:threo ratio was curiously lowered to 3:1. All aldol ratios were determined by NMR integration of the crude reaction mixture because the products underwent substantial decomposition by GC. The acid elimination products were much more stable and were readily determined by GC.

The configurations of the aldol products were determined by spectral comparison of the erythro and threo isomers of **7** which were known.[10] All other Table entries are by analogy. It had been reported that the threo product contained a benzylic CH signal at 4.7 ppm (d of d, J = 3, 8 Hz). We similarly found the threo product contained a benzylic CH at 4.9 ppm (d of d, J = 2, 8 Hz). The erythro product had a benzylic CH at 5.4 ppm (J = 3 Hz), almost identical to the literature value of 5.3 ppm (J = 2.4 Hz). The erythro CHOH resonances in **7** and **13** were more downfield than the threo isomers in the NMR, however, in all other cases the threo CHOH peaks were more downfield. The primary distinguishing stereochemical characteristic in all of these examples was the erythro CHOH coupling was smaller (usually by 2-5 Hz) than the threo CHOH coupling.

The removal of any excess tributyltin hydride and other tin byproducts was most efficiently accomplished by treatment with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) and iodine and rapid filtration through silica gel.[11] The method was found to be very useful, since most of the tin compounds present after the reaction could be removed prior to flash column chromatography.

Because the dehydration products are themselves unsaturated ketones, the feasibility of an additional aldol reaction was possible. A final reaction was attempted using cyclopentanone with heptanal as the first aldehyde which was then eliminated to the alkene **18**. Resubjecting it to the allylic O-stannyl ketyl conditions but using benzaldehyde quench afforded **23** in ca. 40% yield for the three step process.



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General Procedure for Tin Aldol Reaction. An unsaturated ketone (1 equiv), tributyltin hydride (1.1 equiv) and azobisisobutyronitrile (0.2 equiv) were dissolved in benzene (0.5 M) and degassed for 20 min. with Ar. The reaction mixture was then refluxed until starting material was consumed by TLC (*ca.* 4 h). The reaction vessel was next cooled to 10 °C and the appropriate aldehyde (2.0 equiv) was added. The reaction was allowed to stir for 8-12 hrs, concentrated under reduced pressure, and diluted with diethyl ether. Tin residues were removed by Curran's method.[1(e),11] Solids were removed by suction filtration through silica gel and the solution was concentrated and subjected to flash column chromatography to afford the pure aldol products.

General Procedure for Acid Dehydration. The aldol product was dissolved in benzene (0.68 M), and a catalytic amount of *p*-toluenesulfonic acid (spatula tip) was added. The reaction was refluxed in a flask equipped with a Dean Stark tube for 0.5h. The crude mixture was diluted to 3X volume with ether, extracted with sodium bicarbonate (aq. sat.), dried over sodium sulfate, concentrated under reduced pressure, and subjected to flash column chromatography to afford the α,β-unsaturated ketones.

In conclusion, this method represents the only free radical method to introduce one or two carbon substituents by an aldol addition reaction. The overall approach is mild and the conditions are neutral, avoiding classic lithium-ammonia conditions or strong bases like LDA.

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(12) All new compounds have IR, ^{1}H NMR, and combustion analysis consistent with the structure shown.

(13) This ratio could not be accurately determined by crude NMR and was estimated from the chromatographically isolated weights of the erythro and threo products.

(14) The erythro configuration was modestly favored in several ratios which is supported by both Yamamoto's studies[8] and Stille's reactions run at 45 °C.[9] At lower temperatures, the ratio depends on the size of the ligands on tin; for a discussion, see Heathcock, C. H. in *The Aldol Addition Reaction,* in *Asymmetric Synthesis;* Morrison, J. D., Ed., Academic Press, New York, 1984, V. 3, Ch. 2, pp. 142-144.

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