Enantioselective Synthesis of (*R*)- or (*S*)-2-Alkylglutaraldehydic Acid Methyl Esters *via* Chiral Organotin Enamines

Brigitte Nebout, Bernard de Jeso,* and Jean-Claude Pommier

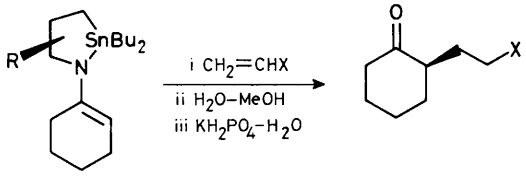
Laboratoire de Chimie des Composés Organiques du Silicium et de l'Etain, Associé au CNRS, UA 35, 351, Cours de la Libération, 33405 Talence Cédex, France

Nucleophilic addition of chiral organotin enamines to electrophilic alkenes is described; a minor modification of experimental conditions gave the other enantiomer of 2-alkylglutaraldehydic acid methyl esters.

Efficient methods of asymmetric synthesis of ketones and aldehydes *via* metallated nitrogen derivatives have been reported by Meyers using chiral lithio-chelated enamines[1,2] and by Whitesell using magnesium salts of imines.[3] Similarly the 'hydrazone method' proposed by Enders leads to a very high enantiomeric excess (e.e.) for both cyclic and acyclic compounds.[4] We recently reported the asymmetric synthesis of α-functionally substituted cyclohexanones by addition of organotin enamines to electrophilic alkenes (Scheme 1).[5]

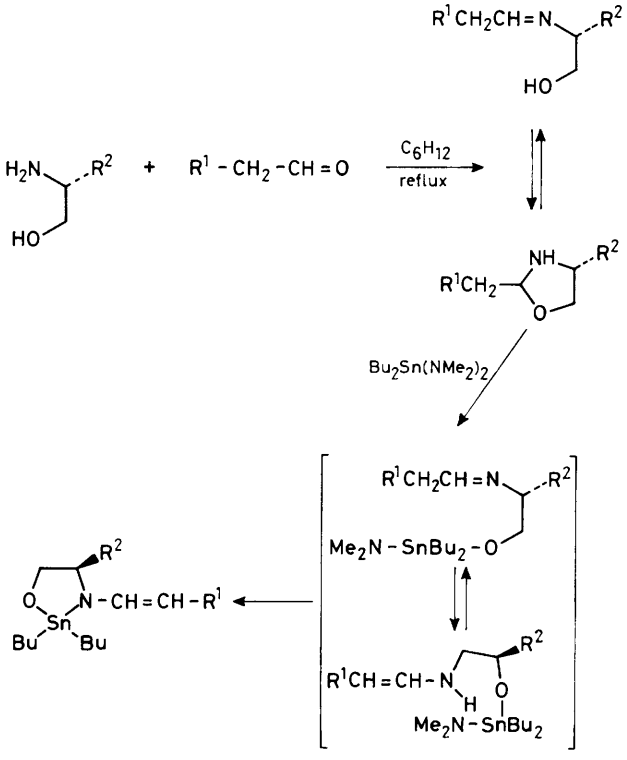
The intermediate metalloenamine exists as a five-membered ring. Since this nucleophile has a definite geometry it can add to electrophilic alkenes with high enantioselectivity. This reaction was investigated and a very high e.e. was observed.[6]

We now decribe the use of chiral organotin enamines in the asymmetric synthesis of acyclic α-substituted carbonyl compounds. Organotin enamines are generated from amino alcohols, aldehydes, and bisdimethylaminodibutyltin *via* a secondary enamine (Scheme 2); reactions were monitored by i.r., ^{1}H n.m.r., and ^{119}Sn n.m.r. spectroscopy.[7]



R = Et, Me; X = CN, CO_2Me

Scheme 1

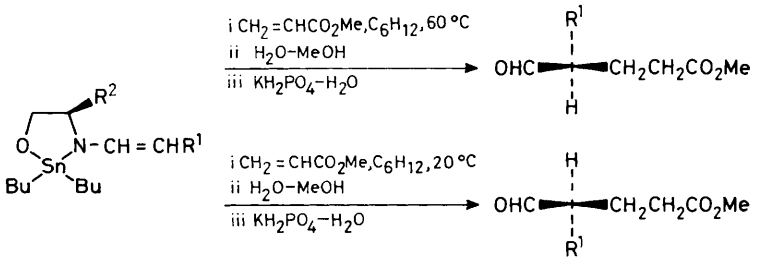


Scheme 2

Table 1. Optically active 2-alkylglutaraldehydic acid methyl esters.

R^1	R^2	Solvent	*T*/°C	Chemical yield/%[a]	$[\alpha]_D^{20}$ [b]	Optical[c] yield/%	Configuration[d]
Pr^i	Et	C_6H_{12}	60	32	+13.2	32	*R*
Pr^i	Et	C_5H_{12}	20	35	−26.5	64	*S*
Et	Et	C_6H_{12}	60	43	+2.0	22	*R*
Et	Et	THF[e]	0	51	−6.0	66	*S*
Me	Et	C_6H_{12}	60	11	+1.6	>8	*R*
Me	Et	C_5H_{12}	20	33	−7.8	37	*S*
Me	Et	THF	0	42	−3.5	17	*S*
Pr^i	Pr^i	C_6H_{12}	60	28	−4.8	>8	*S*
Pr^i	Pr^i	C_5H_{12}	20	40	+16.1	26	*R*
Pr^i	Pr^i	THF	20	58	+9.5	16	*R*
Et	Pr^i	C_6H_{12}	60	28	+3.4	25	*R*
Et	Pr^i	C_5H_{12}	20	30	+1.2	>8	*R*
Me	Et	C_6H_{12}	20	28	−1.64	8	*S*
Et	Et	C_6H_{12}	20	28	−2.54	28	*S*
Pr^i	Et	C_6H_{12}	20	33	−11.4	36	*S*
Pr^i	Et	C_6H_{12}	40	26	+4.90	12	*R*
Pr^i	Et	C_6H_{12}	0	17	−12.8	31	*S*

[a] From the chiral imino alcohol. [b] Experimental results (*c* 5, MeOH). [c] Corrected from the enantiomeric purity of the chiral amino alcohol. [d] Correlated to known 2-alkylglutaric acids. [e] THF = tetrahydrofuran.



Scheme 3

The organotin enamines thus formed at 60 °C or 20 °C are added to methyl acrylate at the same temperature leading to the new optically active 2-alkylglutaraldehydic acid methyl esters (Scheme 3).

As shown in Table 1, the yields and e.e. observed† for acyclic compounds are lower than those reported for cyclic compounds.[5,6] The greater the bulk of the alkyl group, the more selective the reaction. However, the main observation is that a minor modification of experimental procedure has inverted the enantioselectivity of the reaction. Starting from the same chiral auxiliary reagent, [(*R*)(−)2-aminobutanol, e.e. 67%], at 60 °C the aldehyde ester with the *R* enantiomer in excess (*R*/*S* = 66/34) is obtained, at 40 °C the stereoselectivity is reduced (*R*/*S* = 56/44), while at 20 °C the *S* enantiomer is the major product (*R*/*S* = 37/63), with *R*/*S* = 34.5/65.5 at 0 °C.

Chemical yields are low because of the polymerisation of the electrophilic alkene and the isomerization of the organotin enamine to an unreactive organotin imine.

^{119}Sn N.m.r. spectroscopy of the organotin enamine (R^1 = Pr^i, R^2 = Et, C_6H_{12}, +20 °C or +40 °C, Me_4Sn standard) showed a singlet (δ −126 p.p.m.) and a broad band (δ −134.9 to −142.6) corresponding to a 5-co-ordinate species.[8,9] On cooling (0 °C) the broad band became two lines (δ −132.1 and −143.6), which is indicative of a fast equilibrium.‡ The starting spectrum was recovered by heating to +40 °C. Between 40 °C and 20 °C several species are present. There are at least three 5-co-ordinate species, two of them being in fast equilibrium. This equilibrium may account for the effect of the temperature. Alternatively the addition reaction leading to the formation of the organotin enamine may be reversible leading to thermodynamic *vs.* kinetic control of the reaction as is well known for classical enamines.[10]

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† Enantiomeric purity was determined by ^{1}H n.m.r. spectroscopy (90 MHz) in the presence of tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

‡ A singlet (δ −238) appears at 0 °C and increases to a limit of 15% of the total amount of tin at −20 °C. This large upfield shift is indicative of 6-co-ordinated species.