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"DOUBLE ASYMMETRIC REDUCTION" OF (-)MENTHYL BENZOYLFORMATE USING CATALYTIC HYDROSILYLATION

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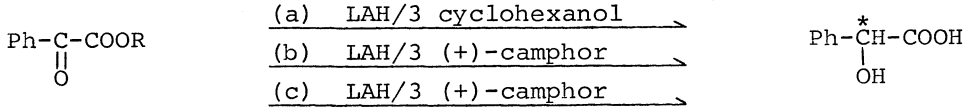
Effective double asymmetric reduction of (-)menthyl benzoylformate was realized using hydrosilylation catalyzed by rhodium(I) complex catalysts. The effect of the (-)menthyl group was estimated.

Asymmetric syntheses of α-hydroxy carboxylic acids have gathered much interest for a long time, and the asymmetric reduction of α-keto esters by catalytic hydrogenation or metal hydride reduction has been extensively studied.[1] Recently, we reported the first and quite effective catalytic asymmetric reduction of α-keto esters[2] using hydrosilylation.[3] Now, we wish to describe in this communication an effective double asymmetric reduction of (-)menthyl benzoylformate using hydrosilylation catalyzed by a rhodium(I) complex with a chiral phosphine ligand.

Conceptually there are several distinct ways in which the asymmetric reduction of an α-keto ester to give the corresponding optically active α-hydroxy ester can be achieved: (a) by the reduction of a chiral ester with an achiral reducing agent: (b) by the reduction of an achiral ester with a chiral reducing agent: (c) by a combination of chiral ester and chiral reducing agent.

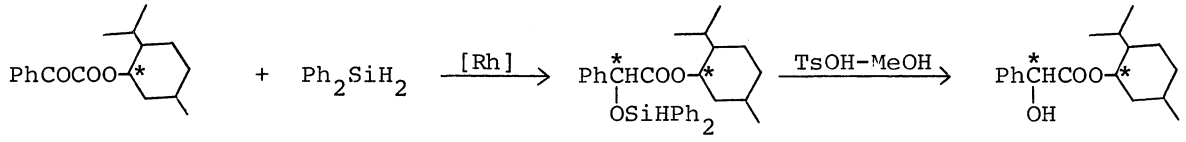
Horeau and co-workers[4] have investigated these possibilities with (-)menthyl benzoylformate and ethyl benzoylformate. Either a simple asymmetric reduction of (-)menthyl benzoylformate with an achiral reducing agent, $LiAlH_4$ (LAH)-cyclohexanol, process (a), or of ethyl benzoylformate with a chiral reducing agent, LAH-(+)-camphor, process (b), gives (R)-(-)-mandelic acid after hydrolysis (10 and 4 % e.e.,



	Optical Yield(% e.e.)	Configuration
(a): R = (-)Menthyl	10	(R)
(b): R = Ethyl	4	(R)
(c): R = (-)Menthyl	49	(R)

respectively). But the "double asymmetric reduction" using both chiral ester and chiral reducing agent, process (c), results in 49 % asymmetric synthesis. This "double asymmetric induction" is higher than would be anticipated on the basis of any simple additive effect. The results made us decide to investigate the "double asymmetric reduction" using hydrosilylation.

We have performed the catalytic asymmetric reduction of benzoylformates by the following ways: (a) a simple asymmetric reduction of (-)menthyl benzoylformate by the hydrosilylation catalyzed by a rhodium complex with achiral phosphine ligands, $(Ph_3P)_3RhCl$: (b) double asymmetric reduction of (-)menthyl benzoylformate using a rhodium complex with a chiral phosphine ligand, [(-)DIOP]Rh(S)Cl (DIOP: 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[5], S = solvent): (c) double asymmetric reduction of (-)menthyl benzoylformate using a rhodium complex with (+)DIOP as a chiral ligands, [(+)DIOP]Rh(S)Cl.



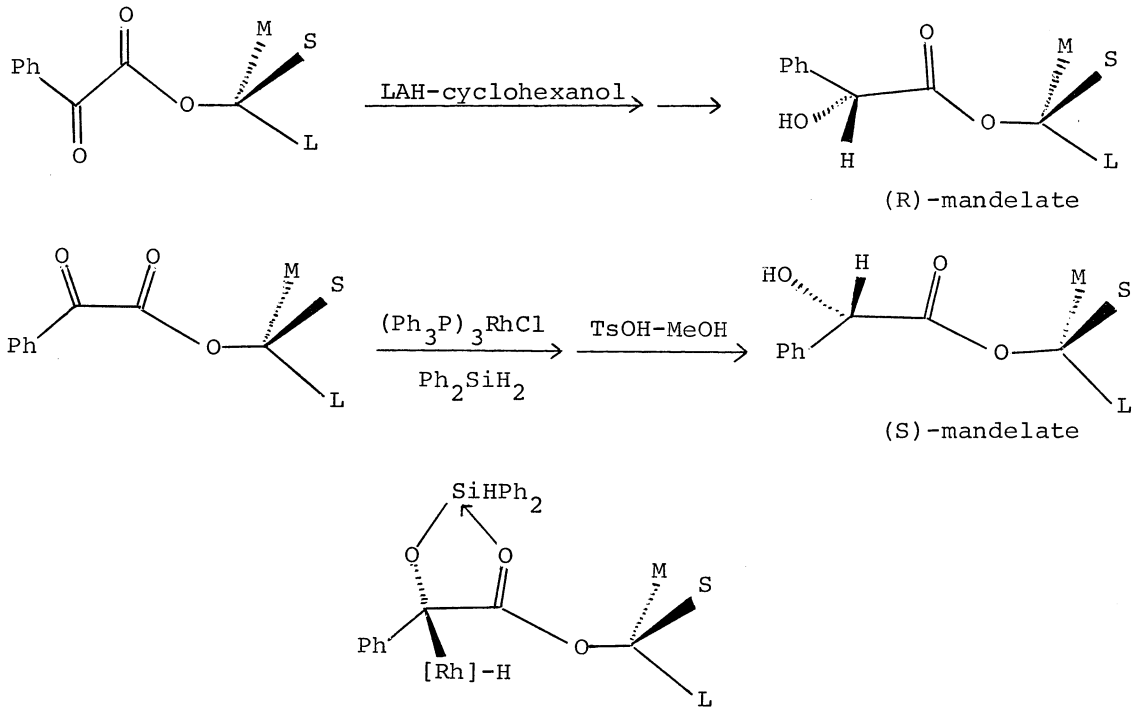
		Optical Yield(% e.e.)	Configuration
(a):	[Rh] = $(Ph_3P)_3RhCl$	32	(S)
(b):	[Rh] = [(-)DIOP]Rh(S)Cl	21	(R)
(c):	[Rh] = [(+)DIOP]Rh(S)Cl	60	(S)

Based on the results from experiment (a), we can estimate the influence of (-)menthyl group on the induction of asymmetry. Namely, the stereochemical control by (-)menthyl group operated to produce (-)menthyl (S)-mandelate. The attained optical yield (32 % e.e.) is considerably higher than that obtained with the use of LAH-cyclohexanol[4]. In an experiment (b), it was shown that the opposing double asymmetric induction by the chiral catalyst and (-)menthyl group afforded (R)-(+)-mandelate with rather low stereoselectivity (21 % e.e.). The rhodium catalyst with (-)DIOP as a chiral ligand, was found to favor the production of (R)-mandelate in this system, and the direction of asymmetric induction was opposite to that by (-)menthyl group. The production of (R)-mandelate was favored in the case of the asymmetric reduction of ethyl benzoylformate with the use of [(-)DIOP]Rh(S)Cl and Ph_2SiH_2 in which the obtained optical yield was very low (1.4 % e.e.) despite the absence of the negative effect of (-)menthyl group. These results clearly indicate that the bulkiness of the ester group is an essential factor for determining the effectiveness and the direction of the asymmetric induction. In an experiment (c), it was demonstrated that the effective double asymmetric induction was realized (60 % e.e.) when the rhodium complex catalyst with (+)DIOP as a chiral ligand was employed as a catalyst, which favored the production of (S)-mandelate. Thus, in this case, the direction of asymmetric induction by [(+)DIOP]Rh(S)Cl well matched to the effect of (-)menthyl group.

As for the effect of (-)menthyl group, the hydrosilylation with the rhodium complex showed an opposite influence on determining the direction of the asymmetric induction compared with LAH-cyclohexanol reduction. Namely, the former favored the formation of (S)-mandelate, while the latter did (R)-mandelate. The latter

case can be well understood by the Prelog's generalization[6] in which the two carbonyl groups of the α-keto ester are in the anti-coplanar conformation.

According to the Prelog's stereochemical consideration, the two carbonyl groups of (-)menthyl benzoylformate should be in the syn-coplanar conformation for the former case. However, it has previously been shown that the stereochemical course of the hydrosilylation catalyzed by a rhodium complex followed a product development control rather than a steric approaching control, and that the reaction proceeded via a silyloxyalkyl rhodium complex.[3c,e,f,h] Consequently, the former results may be best explained by postulating a template effect of the silyl group by chelation which arises from the co-ordination of the remaining carbonyl to the silyl group.[7]



To determine the optical purity of (-)menthyl mandelate we employed the 100MHz NMR spectra of crude reaction mixture in which the methine protons of two diastereomers appeared as well-separated singlets at δ5.00 and δ5.10 in C_6D_6. Thus, we can exclude the possibility of any fractionation during purification process in the estimation of asymmetric induction. The (-)menthyl mandelate which displayed the signal of the methine proton at δ5.10 was found to be the (S)-mandelate since a pure sample of the (S)-mandelate was obtained by the fractional recrystallization of the reduction products using n-hexane, ($[\alpha]_D^{25}$-7.55, c 4.85 in EtOH) and then, the other which showed the methine proton signal at δ 5.00 was identified as (R)-mandelate.

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