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ASYMMETRIC SYNTHESIS OF 2-SUBSTITUTED CYCLOALKANECARBOXALDEHYDES

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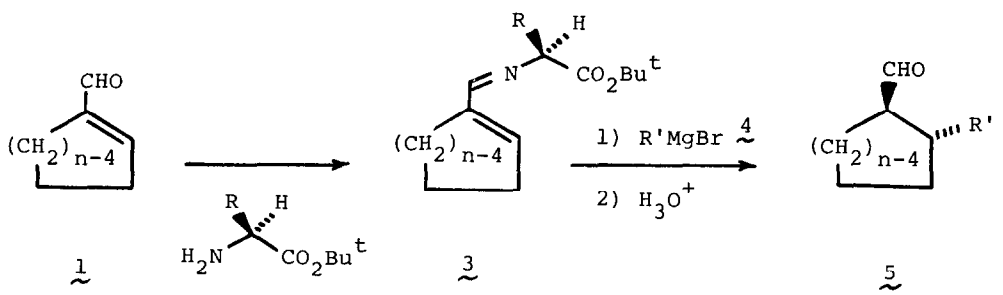
Summary: The 1,4-addition of Grignard reagents to chiral α,β-unsaturated cyclic aldimines (3), prepared from the corresponding cycloalkenecarboxaldehydes (1) and optically active α-amino acid tert-butyl esters (2), was found to give, after hydrolysis, trans-2-substituted cycloalkanecarboxaldehydes (5) in reasonably high enantiomeric purities.

In previous papers,[1] we have developed a novel method for the asymmetric carbon-carbon bond formation in the syntheses of optically active α-amino acids, β-substituted acyclic aldehydes, and α-substituted cyclic ketones in high enantiomeric purities based on the principle of fixing the reactive conformation by forming chelated complex. It is also shown that tert-leucine tert-butyl ester (2, R=t-Bu) is an excellent chiral reagent working as a bidentate ligand. In line with the research on this asymmetric synthetic technique, we next examined the possibility of obtaining a useful method for the synthesis of optically active ring compounds having vicinal two chiral centers. Evaluating such optically active compounds as useful synthons for a variety of biologically active natural products, pharmaceuticals, etc., we report here our preliminary approach to this problem by asymmetric conjugate addition of nucleophiles to chiral cyclic α,β-unsaturated aldimines (3),[2] prepared from cycloalkenecarboxaldehydes (1) and optically active α-amino acid tert-butyl esters (2).

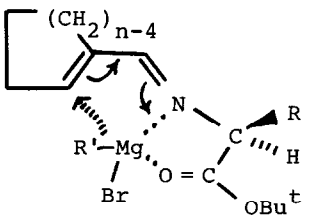


1 L-2 3 5

n=5, 6 ; R=i-Pr, t-Bu ; R'=Ph, $CH=CH_2$

The 1,4-addition of Grignard reagents (4) to the eneimine (3), a chiral enal equivalent, proceeded smoothly to give, after acidic hydrolysis, 2-substituted cyclic aldehydes (5) in reasonable chemical and optical yields. Table summarizes the results of the reaction of 3 with phenyl- and vinylmagnesium bromide. In every case, higher chemical and optical yields were obtained for the eneimines derived from tert-leucine tert-butyl ester (2, R=t-Bu) than those derived from valine tert-butyl ester (2, R=i-Pr). It is also shown that aldehydes (5) having trans-configuration were obtained exclusively (except for runs 7 and 8), probably due to the epimerization of the initially formed cis-isomer during acid hydrolysis as described by Corey in similar ring systems.[3] In runs 7 and 8, the product was a mixture of almost equal amounts of cis- and trans-isomer, but could be epimerized to a mixture predominating in trans-isomer by treatment with conc. HCl in THF according to the reported procedure.[3] The optical purities and absolute configuration of the products were determined by chemical correlation with the known compounds.

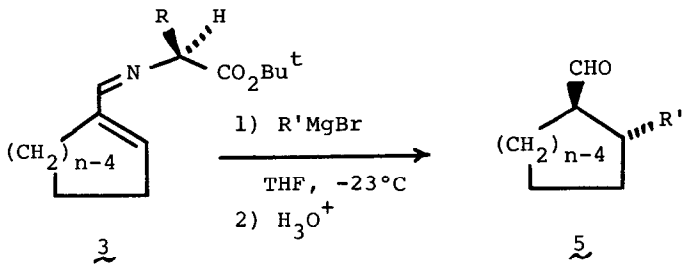
It should be noted that the absolute configuration of the products obtained by the present method using L-2 as a chiral reagent was as shown in 5. It should also be mentioned that in cases where tert-leucine tert-butyl ester (2, R=t-Bu) was used as a chiral reagent, the optical yields of the products were very high and the chiral reagent was recovered in good yield without any loss of optical purity for reuse. The stereochemical course of the present 1,4-addition reaction can be predicted by the previously proposed mechanism[1] as shown in 6, i.e., carbon nucleophile attacks from the less hindered side of the complex.



6

Typical procedure is as follows.

(1R,2S)-(-)-trans-2-Vinylcyclopentanecarboxaldehyde (5, n=5, R'=CH=CH$_2$) (run 4) ——— A solution of vinylmagnesium bromide in THF (20 ml, 41 mmole) was added dropwise to a cooled (-23°C) solution of α,β-unsaturated aldimine (3, n=5, R=t-Bu) (2.65 g, 10 mmole) (prepared from 1 (n=5) and L-2 (R=t-Bu) (α_D^{20} +1.522° (l=0.03, neat), corresponding to be 90.6% optically pure[1e])) in THF (50 ml) under argon. After 5 hr of stirring at -23°C, the reaction mixture was poured into an ice-cooled 10% aqueous citric acid (60 ml), stirred at room temperature for 1 hr, and the whole was extracted with ether (100 ml x 2). The combined



3 5

Run	n	R	R'	Isolated yield %	e.e. %
1	5	i-Pr[b]	Ph	72	61[e] (56)[j]
2	5	t-Bu[c]	Ph	82	82[e] (77)[i,j]
3	5	i-Pr[b]	$CH=CH_2$	36	71[f]
4	5	t-Bu[c]	$CH=CH_2$	69	92[f,i]
5	6	i-Pr[b]	Ph	52	49[g] (50)[j]
6	6	t-Bu[c]	Ph	54	91[g] (88)[i,j]
7[a]	6	i-Pr[b]	$CH=CH_2$	31[d] (trans/cis=80/20)	69[h]
8[a]	6	t-Bu[c]	$CH=CH_2$	68[d] (trans/cis=87/13)	93[h,i]

[a]The reaction was carried out at 0°c. [b]Optically pure L-2 (R=i-Pr) was used. [c]L-2 (R=t-Bu) of 90.6% optical purity was used. [d]A mixture of trans- and cis-isomer after epimerization of the initial product by the reported procedure.[3] [e]Based on $[\alpha]_D^{20}$ -76.8° (benzene) for optically pure 5 (n=5, R'=Ph) by chemical correlation with (1R,2R)-trans-cyclopentane-1,2-dicarboxylic acid.[4] [f]Based on $[\alpha]_D^{20}$ -57.9° (acetone) for optically pure 5 (n=5, R'=$CH=CH_2$) by chemical correlation with (1R,2R)-trans-cyclopentane-1,2-dicarboxylic acid.[4] [g]Based on $[\alpha]_D^{20}$ -37.8°(benzene) for optically pure 5 (n=6, R'=Ph) by chemical correlation with (1S,2S)-trans-2-phenylcyclohexanecarboxylic acid.[5] [h]A value for trans-isomer. This value was obtained by chemical conversion to (1R,2R)-trans-cyclohexane-1,2-dimethanol, whose maximum rotation is reported to be $[\alpha]_D^{20}$ +21.4°(benzene).[6] [i]Corrected for the optical purity of L-2 (R=t-Bu) used. [j]Values in parentheses were obtained by PMR analysis of the derivatives using chiral shift reagent [Eu(hfc)$_3$].

extracts were washed with satd. aqueous $NaHCO_3$ (50 ml) and brine (50 ml x 2) successively, and dried over $MgSO_4$. Evaporation of the solvent at ordinary pressure followed by column chromatography (silica gel, hexane/ether=15/1) gave the objective aldehyde (5, n=5, R'=CH=CH_2) (860 mg, 69%) as a faint yellow oil of $[\alpha]_D^{20}$ -48.0°(c=1.10, acetone). IR (film, cm^{-1}): 2720, 1725, 1640; PMR ($CDCl_3$, δ): 4.8-5.2 (2H, m), 5.6-6.0 (1H, m), 9.54 (1H, d, J=2.5 Hz). The above aqueous citric acid solution was basified with K_2CO_3, and the whole was extracted with benzene (50 ml x 2). The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave L-2 (R=t-Bu) (1.18 g, 63%) of α_D^{20} +1.522 (l=0.03, neat).

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