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ASYMMETRIC SYNTHESIS OF 1,2-DISUBSTITUTED CYCLOALKANECARBOXALDEHYDES. PROCEDURES FOR THE HIGHLY STEREOSELECTIVE PREPARATION OF cis- AND trans-ISOMER

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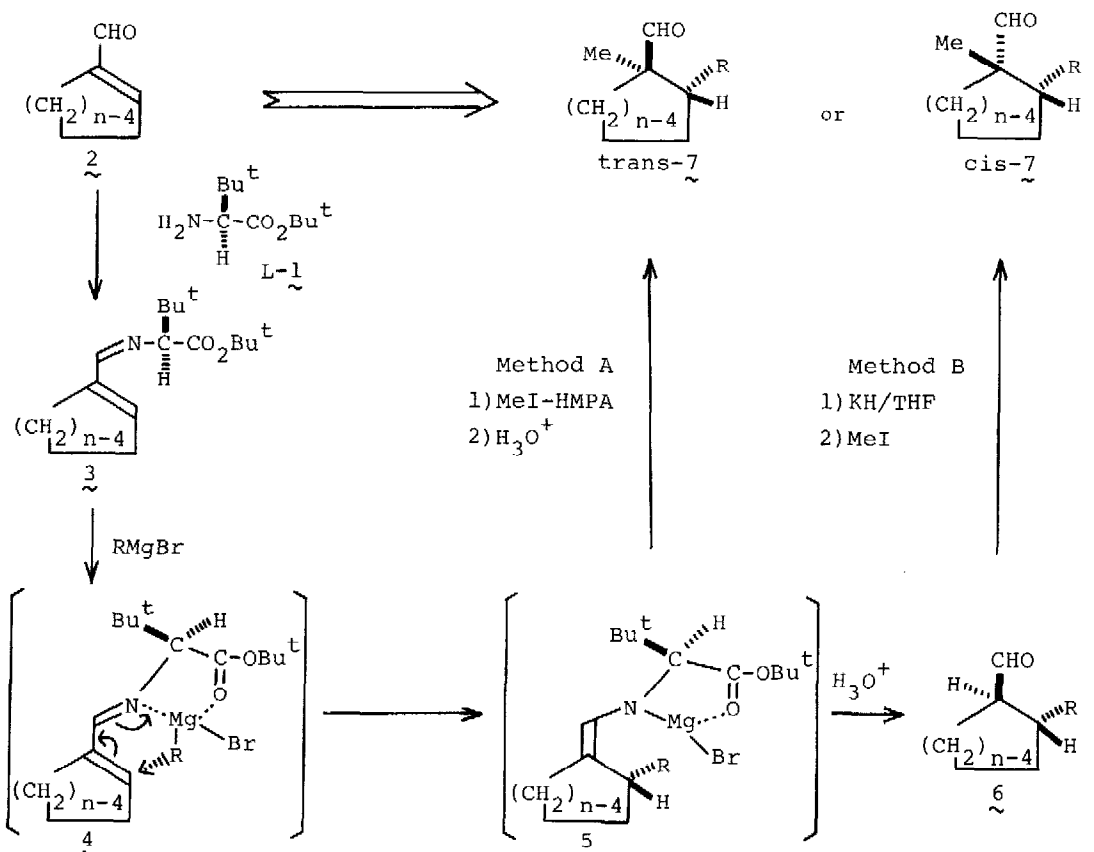
Summary: Procedures for the asymmetric synthesis of 1,2-disubstituted cycloalkanecarboxaldehydes (7) having asymmetric tertiary and quaternary carbon atoms in vicinal positions from the corresponding cycloalkenecarboxaldehydes (2) in high diastereomeric and enantiomeric purities are described.

As part of our research program directed toward the development of new stereoselective reactions by the strategy of fixing the reactive conformation by chelation,[1] we have reported a highly efficient method for the asymmetric synthesis of trans-2-substituted cycloalkanecarbox-



aldehydes (6)(82 – 93% e.e.) by the 1,4-addition of Grignard reagents (phenyl- and vinyl-magnesium bromide) to chiral α,β-unsaturated aldimines (3), prepared from the corresponding cycloalkenecarboxaldehydes (2) and optically active tert-leucine tert-butyl ester (1), followed by hydrolysis of the resulting magnesioenamines (5).[1g] It is shown that optically active amino ester (1) is an excellent chiral auxiliary reagent, working as a bidentate ligand to fix the conformation by chelation during the reaction, and being recovered without any loss of optical purity for recycling after the reaction.

Based on the mechanistic consideration proposed earlier,[1g] it is reasonable to assume that the conformation of magnesioenamines (5) prepared by the above method is also fixed in particular geometry (Z-stereochemistry around the enamine double bond), and therefore, alkylation of these enamines (5) holds the possibility to be effected again with high stereoselectivity. Evaluating the utility of optically active and diastereomerically pure cycloalkane derivatives having vicinal chiral centers in their rings as synthons, we have now extended our studies to the asymmetric synthesis of 1,2-disubstituted cycloalkanecarboxaldehydes (7) by two methods as shown in the Chart. Thus, in method A, the reaction was performed by one-pot procedure via Grignard 1,4-addition to the chiral aldimines (3) in THF (-23°, several hr) as reported previously[1g] followed by alkylation of the resulting magnesioenamines (5) with methyl iodide (6 eq.) in THF in the presence of HMPA (4 eq.) (-23° for 2 hr and at room temperature for 16 hr). In method B, the aldehyde (6) obtained as reported previously[1g] was metalated with potassium hydride (2 eq.) in THF (room temperature) and then alkylated with methyl iodide (4 eq.) (-23°, 0.5 hr) as usual. The relative configuration of the products were determined by ^{13}C-NMR chemical shift values of C-methyl groups,[3] and was further confirmed for cyclohexane derivatives by chemical correlation to the known dicarboxylic acids (cis-8,[4,5] trans-8,[4] cis-9,[6] trans-9[7]) using racemates.[8]

The results are summarized in the Table (run 1~8). It is quite surprising to note that diastereoselectivity of the reaction by method A (except run 1) is highly different to that by method B.

The stereochemical course of the first conjugate addition step by nucleophile (RMgBr), a common step for both method A and B, is already well known.[1g] The question in the present study is the stereochemical course of the second alkylation step by electrophile (MeI), which decides diastereoselectivity of the reaction. The fact that methylation of enolate anion of 6 by method B occurs preferentially from the opposite side of initially introduced R-group to give cis-isomer is quite reasonable based on the estimation of steric effect of the R-group. Therefore, some other factors should be operative at the methylation of magnesioenamine (5) by method A, where reaction occurs preferentially from the same side of the R-group. One of the possible factors for this reversal of the stereochemical course by method A is considered to be the steric effect by the original chiral center (tert-leucine tert-butyl ester moiety) in a fixed Z-configuration of magnesioenamine as shown in 5. The result of run 1 by method A might be due to the consequence of the sum of at least the above two opposing effects, among which the effect of more bulky phenyl group attached to five membered ring predominates.

The importance of Z-configuration of magnesioenamine (5) upon diastereoselectivity to give trans-isomer was further demonstrated by the following experiments. It is expected that E-Z

Table Asymmetric Synthesis of 1,2-Disubstituted Cycloalkanecarboxaldehydes (7)

Run	Method[a]	n	R	Chemical yield(%)[b] trans-7	cis-7	% e.e.[c,e]
1	A	5	C_6H_5	15	62	82
2	A	5	CH_2=CH	62	0	92
3	A	6	C_6H_5	55	0	91
4	A	6	CH_2=CH	67	0	93
5	B	5	C_6H_5	0	65	82
6	B	5	CH_2=CH	0	61	92
7	B	6	C_6H_5	1	62	91
8[d]	B	6	CH_2=CH	11	51	93
9	C	5	C_6H_5	2	44	82
10	C	6	C_6H_5	0	49	91

a) See text. b) Isolated yield after column chromatography. In runs where method B was employed, some O-methylated product was also isolated. c) Corrected value for 91% optical purity of L-1 used. d) Methylation was perfomed at-50° for 2hr. e) Absolute configuration of 7 was determined based on that of 6. See reference 1g.

isomers of metalloenamines do not equilibrate under the condition employed by method A,[9] but do equilibrate in THF under reflux.[10] Assuming that magnesioenamine (5) having Z-configuration is a less stable isomer compared with the corresponding E-isomer, it is probable that equilibration of 5 prior to alkylation will change the diastereoselectivity of the reaction. Therefore, method C was introduced where the reaction mixture was heated to reflux for 3 hr just before methylation at-23° in method A. Although the yields became lower due to the instability of magnesioenamines, the reaction was found to give cis-isomer prefrentially as predicted (run 9, 10).

The procedures described above give promise for the synthesis of cis- and trans-isomer of 1,2-disubstituted cycloalkanecarboxaldehydes in high diastereomeric and enantiomeric purities. Investigations along this line including precise mechanism of the reaction are now in progress.

References and Notes

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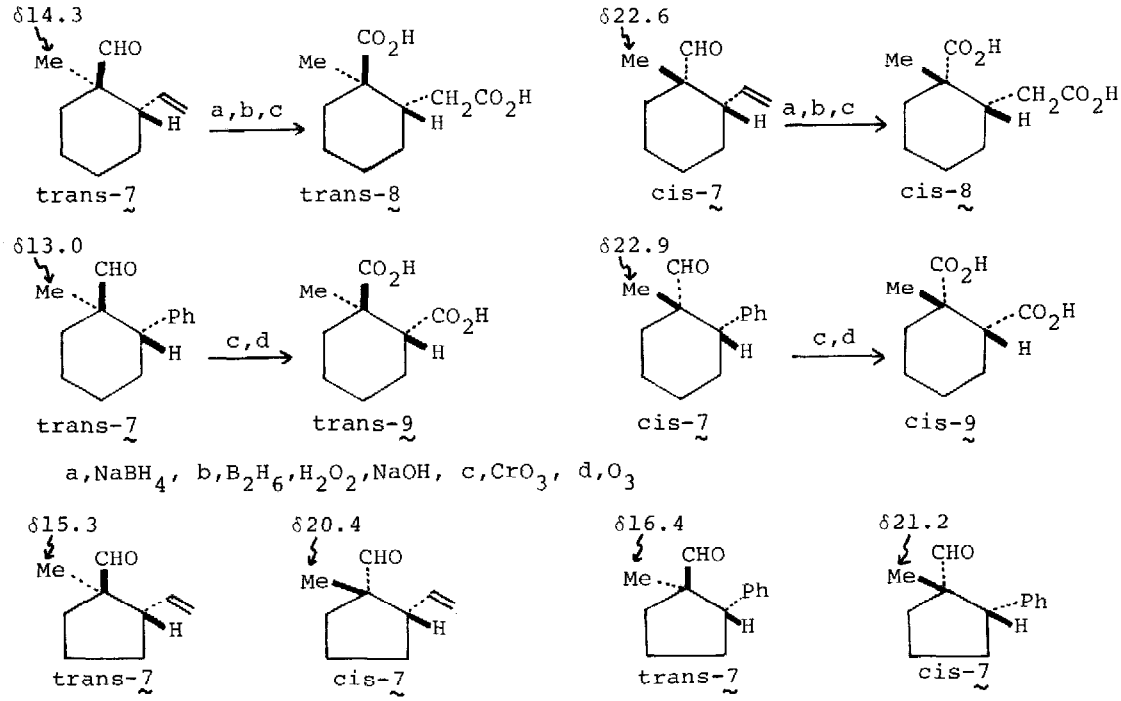

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