A Highly Stereoselective Reduction of Substituted Cyclohexanones Using Triisobutylaluminum–Amine Complexes

Toshimitsu SUZUKI, Maki ITOH,* Shigeyuki OGAWA, and Yoshinobu TAKEGAMI

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606

(Received February 23, 1978)

The stereochemistry of the reduction of substituted cyclohexanones with a triisobutylaluminum(TIBA)–amine complex has been investigated, and the origin of the stereoselectivity has been discussed. Although a reduction of 4-*t*-butylcyclohexanone with free TIBA at 60 °C gave 83% *trans* alcohol, with a high stereoselectivity, 91—98% *trans* alcohol was obtained in this study. In order to discuss the reactivity of the reagent, the mode of the complexing of an amine to TIBA was investigated by infrared and NMR spectroscopy.

The stereochemistry of the reduction of substituted cyclohexanones has been investigated by many workers, and there have been a large number of discussions about factors controlling stereoselectivity.[1] Eliel *et al.*[2] reported the reduction of 4-*t*-butylcyclohexanone with $LiAlH_4$ to give 91—93% *trans*(OH equatorial) alcohol. Recently Ashby[3] reexamined the reduction of the same ketone with several metal hydrides and demonstrated it to give 86—92% *trans* alcohol in THF. Eliel *et al.*[2] reported the epimerization equilibrium of 4-*t*-butylcyclohexanol with aluminum isopropoxide in 2-propanol, resulting in 79% *trans* and 21% *cis* isomers.

The origin of stereochemical controls was first reported by Dauben *et al.*,[4] who suggested two concepts, *i.e.*, "product development control" and "steric approach control." On the other hand, Chérest and Felkin[5] considered "steric strain" and "torsional strain" as alternatives to these concepts. Richer[6] proposed that steric interactions take place between the entering group and 3,5-axial hydrogens.

The reduction of substituted cyclohexanones with triisobutylaluminum (TIBA) was studied by Haubenstock[7] and Ashby,[8] who reported interesting stereochemical results. In this experiment, the reduction of 4-*t*-butylcyclohexanone and other substituted cyclohexanones with a TIBA–amine complex was investigated, and the changes in the stereoselectivity were discussed. A remarkable change in the product distribution was observed. Recently Mukaiyama *et al.*[9] reported a selective reduction of carboxamides to aldehydes with aluminum diamide hydrides.

Experimental

Materials. The toluene was distilled over calcium hydride and stored under an argon atmosphere.

4-*t*-Butylcyclohexanone prepared by the oxidation of 4-*t*-butylcyclohexanol[10] was purified by vacuum distillation (93 °C/10 Torr).

The pyrrole, piperidine, and aniline were purified by vacuum distillation.

The triisobutylaluminum(TIBA) and triethylaluminum (TEA) were purified by vacuum distillation and prepared as about a 1 M toluene solution. The concentration of the solution was determined by titration using EDTA·2Na.

The 3,3,5-trimethylcyclohexanone, 2,2,6-trimethylcyclohexanone, camphor, norcamphor, diphenylamine, dicyclohexylamine, diethylamine, pyrrolidine, benzylamine, octylamine, triethylamine, triphenylamine, and *N*,*N*-dimethylaniline were commercially available reagents and were used without further purification.

Ketones and amines were used as 1 M toluene solutions, which were stored over "Drierite"(calcium sulfate) or calcium hydride.

Procedure. The following procedure for the reduction of a ketone is representative. A three-necked flask equipped with a magnetic stirrer, a gas inlet, a self-sealing rubber cap, and a gas outlet connected to a bubbler was flushed with argon. Eight ml of toluene and 1 ml (1 mmol) of an amine solution were then introduced into the flask at 0 °C, after which 1 ml(1 mmol) of a TIBA solution was stirred in. After a three-hours' reaction, 1 ml (1 mmol) of a ketone solution was added, and then the reaction was carried out at 60 °C. After a certain reaction time, the reaction mixture was hydrolyzed with a small piece of ice and the aluminum hydroxide was removed. Then the solution was extracted with ether, and the ether solution was dried over "Drierite". GLC(Hitachi model F6-D with a Golay R45 column) was employed for the qualitative and quantitative analyses.

Results and Discussion

Various amines were selected for use in the modification of TIBA, and the reductions of 4-*t*-butylcyclohexanone(4*t*BC) and several substituted cyclohexanones were investigated. The results of the reductions of ketones with amine-modified TIBA and free TIBA at 60 °C in toluene are shown in Table 1.

In the case of 4*t*BC, as the conformation of the cyclohexane ring is fixed by the bulky 4-*t*-butyl group, the stereochemistry of the reduction will be discussed only in terms of the steric requirement of the reducing agent. When 4*t*BC was reduced with free TIBA at 60 °C, 83% *trans* alcohol was obtained. This is almost an equilibrium composition of two isomeric alcohols. When diphenylamine, dicyclohexylamine, pyrrole, triethylamine, or *N*,*N*-dimethylaniline was used as an amine, the reduction of 4*t*BC proceeded quantitatively, and 91—98% *trans* alcohol was obtained. In contrast to this, the reaction hardly proceeded at all with TIBA–piperidine, pyrrolidine, benzylamine, or octylamine system.

3,3,5-Trimethylcyclohexanone(335TMC) introduces a methyl group in the 3-axial position which hinders axial attack strongly. An equatorial attack of $LiAlH_4$ predominates to give 75—80% OH axial alcohol.[3] However, in the reduction of 335TMC with TIBA, the diisobutylaluminum 3,3,5-trimethylcyclohexyl oxide undergoes epimerization to give 99.7% OH equato-

Table 1. Reduction of Substituted cyclohexanones with a TIBA–amine system[a]

Run	Amine	Time (h)	Unreac. ketone (%)	Products (%)[b] OH ax.	OH eq.
4-*t*-Butylcyclohexanone					
1	——	3.0	2	17	83
2	——	3.0	64.5	29.8	70.2[c]
3	Diphenylamine	0.5	14	15	85
		2.0	1	4.5	95.5
4	Dicyclohexylamine	2.0	0	2	98
5	Pyrrole	2.0	0.5	4.5	95.5
6	Diethylamine	2.0	13	30	70
7	Piperidine	2.0	100	0	0
8	Pyrrolidine	2.0	100	0	0
9	Aniline	3.0	79	39	61
10	Benzylamine	3.0	100	0	0
11	Octylamine	3.0	≃100	0	trace
12	Triethylamine	3.0	6	6	94
13	Triphenylamine	3.0	9	18	82
14	*N,N*-Dimethylaniline	3.0	15	9	91
3,3,5-Trimethylcyclohexanone					
15	——	2.0	32.5	82.7	17.3[d]
		31.0	30.7	0.3	99.7[d]
16	Diphenylamine	2.0	31	40	60
		24.0	26	0	100
17	Pyrrole	2.0	15	30	70
		24.0	6	0	100
18	Diethylamine	2.0	20	67	33
		24.0	15	7	93
2,2,6-Trimethylcyclohexanone					
19	——	3.0	52	61	39[c]
20	Diphenylamine	24.0	22	56	44
		48.0	22	50	50
Camphor				(OH exo)	(OH endo)
21	——	3.0	11	87	13
22	Dicyclohexylamine	3.0	≃0	87	13
23	Aniline	3.0	41	90	10
Norcamphor					
24	——	3.0	50	7	93
25	Dicyclohexylamine	3.0	≃0	7	93

a) The reaction was carried out in a 1:1:1 ratio of an amine, TIBA, and a ketone at 60 °C in toluene. b) The isomeric alcohols produced are standardized at 100%. c) Reaction at 0 °C. d) Ref. 7. Reaction at 41 °C in benzene.

rial alcohol during the prolonged reaction time.[8] In this study, at an early stage of the reaction 30—70% OH axial alcohol was obtained, depending on the amine employed. Also, during the course of a prolonged reaction, isomeric aluminum alkoxide underwent epimerization to give OH equatorial alcohol almost entirely.

As 2,6-methyl groups(axial and equatorial) hinder the reaction at the carbonyl group in the reduction of 2,2,6-trimethylcyclohexanone (226TMC), the rate of reduction was very slow and the stereoselectivity was not seen; that is, a 1:1 mixture of isomeric alcohols was obtained after 48 h reaction. 61% OH axial alcohol was obtained in the reduction with TIBA itself at 0 °C.

An attack from the less hindered side was seen in the reduction of camphor and norcamphor, and the reaction proceeded almost 100% with the dicyclohexylamine–TIBA system. The stereoselectivity was the same as in the reduction with free TIBA.

As has been shown above, an improvement in the stereoselectivity using amine-modified TIBA compared with the case of the reduction with free TIBA was observed in the reduction of 4*t*BC, which has not so severe a steric hindrance as the other ketones used in this study.

The results of the reductions of 4*t*BC and 335TMC using an excess of TIBA–amine reagent are shown in Table 2. The reduction of 4*t*BC with a threefold quantity of TIBA–diphenylamine gave 55% *cis* alcohol. Reduction with excess TIBA did not change the products distribution compared with the 1:1 reaction of TIBA and 4*t*BC at 0 °C. The reduction of 335TMC with a threefold quantity of TIBA and diphenylamine gave 93% OH axial alcohol even after 24 h reaction.

Table 2. Reduction of 4*t*BC and 335TMC with different TIBA–amine–ketone ratios[a]

Run	Amine	Time (h)	Unreac. ketone (%)	Products (%)[b] OH ax.	OH eq.
4-*t*-Butylcyclohexanone					
26	——	3.0	24.4	28	72[c]
27	Diphenylamine	2.0	26	55	45
28	Dicyclohexylamine	3.0	5	36	64
29	Piperidine	3.0	≃100	0	trace
30	Aniline	3.0	80	46	54
3,3,5-Trimethylcyclohexanone					
31	Diphenylamine	2.0	45	93	7
		24.0	27	93	7

a) The reaction was carried out in a 3:3:1 ratio of an amine, TIBA, and a ketone at 60 °C in toluene. b) The isomeric alcohols produced are standardized at 100%. c) Reaction in a 2:1 ratio of TIBA and a ketone at 0 °C. Ashby reported 60% *trans* alcohol in 1:1, 2:1, and 5:1 ratios of TIBA and 4*t*BC, and 70% *trans* alcohol in a 1 : 2 ratio at 22 °C in benzene.

IR Spectroscopy of the TIBA–Amine–4tBC System. With respect to TIBA and diphenylamine, Neumann[11] reported that an aluminum amide was not produced at room temperature, but was produced slowly at 50 °C and rapidly at 80 °C. In this study, the reaction of TIBA with an amine was carried out at 0 °C; an aluminum amide was not formed, however.

The infrared spectral data of TIBA–amine–4*t*BC systems are given in Table 3. When diphenylamine was added to TIBA in toluene at room temperature, the ν_{NH} of the amine shifted to a lower frequency, *i.e.*, from 3430 to 3200 cm^{-1}. This indicates that a TIBA–amine complex is formed. When 4*t*BC was added to this complex, ν_{NH} appeared at 3430 cm^{-1} and $\nu_{C=O}$ was not observed. When the reaction of TIBA

Table 3. IR characteristic absorptions of TIBA–amine–ketone systems in toluene[a)]

Sample	ν_{NH} (cm^{-1})	$\nu_{C=O}$ (cm^{-1})
Free 4*t*BC	—	1720, sharp
Free diphenylamine	3430, sharp	—
Diphenylamine + TIBA	3200, broad	—
Diphenylamine + TIBA + 4*t*BC	3430, sharp	not observed
Free piperidine	3310, broad	—
Piperidine + TIBA	3230, sharp	—
Piperidine + TIBA + 4*t*BC	3230, broad	1640, broad

a) Reaction carried out at room temperature. $[TIBA]_0 = 1.0$ M.

and diphenylamine was carried out at 60 °C for 4 h, the ν_{NH} disappeared, thus indicating the formation of aluminum amide.

The reduction of 4*t*BC with the TIBA–piperidine system was completely interupted. The IR data of this system exhibits a red shift of ν_{NH} from 3310 cm^{-1} to 3230 cm^{-1}, indicating the formation of a complex. The addition of 4*t*BC to this complex, however, did not change the ν_{NH} frequency. In addition, a broad absorption at 1640 cm^{-1} due to $\nu_{C=O}$, which was at a frequency 80 cm^{-1} lower than that of free 4*t*BC in toluene was observed. These findings indicate that the amine and the ketone are complexed to TIBA at the same time; that is, the ketone added to the TIBA–amine complex coordinates to TIBA, but the amine was not liberated from the complex as in the case of the results described above.

^1H NMR Spectroscopy of TEA–Amine Systems. In order to discuss the difference in the reactivity of TIBA–amine complexes, ^1H NMR studies were carried out. Triethylaluminum(TEA)–amine systems were employed instead of TIBA–amine systems. The internal shifts of the CH_3–CH_2 group in various TEA–amine systems are given in Table 4. In general, the internal shift($\Delta\delta$) of the ethyl derivative, CH_3–CH_2–X, is proportional to the electronegativity of the substituent, X.[12)] A larger value of $|\Delta\delta|$ means a stronger coordination of an amine to TEA. The internal shift, τ_{CH_3}-τ_{CH_2}, of free TEA was −0.80 ppm, while those of the piperidine and pyrrolidine complexes were −1.33 ppm. Those of the diphenylamine and pyrrole complexes were −0.93 and −0.83 ppm respectively. In the case of the aniline complex, a sharp peak appeared at δ 0.97, indicating the formation of ethane and an aluminum amide. Triphenylamine seems to be difficult to coordinate to TEA because of its bulkiness, so the value of the internal shift was not changed. The reduction of 4*t*BC with the TIBA–triphenylamine system gave 82% *trans* alcohol, similar to the result of the reduction with free TIBA.

Table 4. Internal shifts of the ethyl group in various TEA–amine systems[a)]

Amine	τ_{CH_3}-τ_{CH_2}	Difference from free TEA	pK_b of Amine
——	−0.80	0	
Piperidine	−1.33	−0.53	2.80 (in water)
Pyrrolidine	−1.33	−0.53	2.7[b)]
Diphenylamine	−0.93	−0.13	13.2
Pyrrole	−0.83	−0.03	13.6
Aniline	−0.80	0	9.40 (in water)[c)]
Triphenylamine	−0.80	0	

a) 60 MHz ^1H NMR in C_6D_6; shifts in ppm. b) Ref. 13. c) Ref. 14.

Meanwhile, the pK_b values of amines are correlated with the internal shrfts; *i.e.*, the basicity is not so strong in diphenylamine and pyrrole, but is very strong in piperidine and pyrrolidine.

The coordination between Al and N being strong for an amine such as piperidine, the amine cannot be liberated from the TIBA–amine complex upon the addition of a ketone. Thus, the ketone cannot coordinate to TIBA enough to undergo subsequent reduction. When the Al–N coordination is moderately strong, the amine is liberated from the TIBA–amine complex upon the addition of a ketone; then a high selectivity is obtained. Moreover, triphenylamine showed no effect in selectivity because of the difficulty of complexing; this result is the same as in the reduction with free TIBA.

In the reduction of 4*t*BC with TIBA–diphenylamine, in which the reaction of TIBA and the amine was carried out at 60 and 80 °C, about 50% 4*t*BC was reduced to give 74 and 83% *trans* alcohol respectively. Thus, the formation of an aluminum amide decreases the reactivity and the stereoselectivity. The addition of diphenylamine to the reaction mixture of 4*t*BC and TIBA did not change the composition of isomeric alcohols. The high selectivity to *trans* alcohol was caused by the complexation of an amine to TIBA and the liberation of the amine from the complex upon the addition of a ketone, and not by the formation of an aluminum amide.

As is shown in Table 2, when excess TIBA–amine was allowed to reduce 4*t*BC or 335TMC, a larger amount of OH axial alcohol was produced compared with the case of the equimolar reaction of TIBA–amine to a ketone. In these ketones, OH axial alcohol is produced by the attack from the less hindered side; *i.e.*, the equatorial attack that was seen in the reduction of camphor and norcamphor. Especially in the reduction of 335TMC, 93% OH axial alcohol was produced, irrespective of the reaction time, with a three-fold quantity of TIBA–diphenylamine. On the other hand, 100% OH equatorial alcohol was produced after 24 h with equimolar TIBA–diphenylamine. As is shown in the reduction of 335TMC with TIBA at 41 °C in benzene, 82.7% OH axial alcohol was obtained after 2 h, while 99.7% OH equatorial alcohol was obtained in 31 h(Table 1, Run 15). Thus, diisobutylaluminum 3,3,5-trimethylcyclohexyloxide undergoes epimerization to a more stable isomer remarkably well. This epimerization was scarcely observed in an excess of TIBA–amine to the 335TMC system. The results of the reduction of 335TMC with excess TIBA–

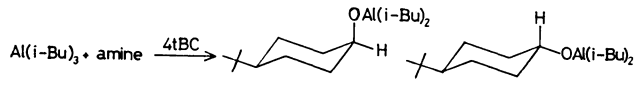
amine show the net steric course of the reducing agent to this ketone; the subsequent epimerization is almost suppressed. The result, 93% OH axial alcohol, is highly stereoselective compared with that in the reduction with $LiAlH_4$ in THF, which gives 75—80% OH axial alcohol.[2]

Considering the suppression of epimerization using an excess of a TIBA–amine reagent, the 55% OH axial alcohol obtained in the reduction of 4*t*BC with a threefold quantity of TIBA–diphenylamine shows stereoselectivity at the point of the attacking of the reducing agent. When one-to-one TIBA–amine to 4*t*BC was used, however, a great amount of OH equatorial alcohol was obtained.

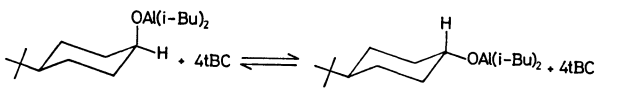
It is also noteworthy that the reaction was almost completed in 2 or 3 h when an equimolar amount of TIBA–amine to a ketone was used, while a large quantity of unreacted ketone existed in the presence of an excess of the TIBA–amine complex. Therefore, the completion of the reaction seems to be one of the factors in the epimerization to a more stable isomer.[15] In the reduction of 4*t*BC with free TIBA, however, the reaction also proceeded almost quantitatively to give only 83% *trans* alcohol.

When the reaction time was 0.5 h in the reduction of 4*t*BC with an equivalent amount of TIBA–diphenylamine, unreacted 4*t*BC remained and the *trans* alcohol was 85%. Even if the remaining 14% of 4*t*BC is allowed to be reduced only by axial attack, the amount of *trans* alcohol cannot reach 95.5%, the result after a reaction time of 2 h. The high selectivity to *trans* alcohol may be interpreted not only by the steric requirement of the transition state, but also by the enhancement of the reaction rate and epimerization. This is more marked in the reduction of 335TMC.

As has been mentioned above, when a TIBA–amine reagent was used in an amount equimolar to a ketone, epimerization between diisobutylaluminum alkoxide of *cis*- and *trans*-4-*t*-butylcyclohexanol occurred; it was promoted further in the presence of an amine (Eqs. 1 and 2). Consequently, 95—98% *trans* alcohol was obtained after hydrolysis.



(1)



(2)

When a large excess of a TIBA–amine reagent was used, the amount of the least stable axial alcohol increased and a large amount of unreacted ketone was found. This means that the reduction of the ketone and the epimerization of the diisobutylaluminum alkoxide that produced are suppressed by an excess of a TIBA–amine complex. This unusual behavior of the reagent cannot be interpreted at present, indicating that the characteristics of the reagent are more complicated than those of a usual reducing agent such as $LiAlH_4$.

References

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, New Jersey (1971).
2) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).
3) E. C. Ashby and J. R. Boone, *J. Org. Chem.*, **41**, 2890 (1976).
4) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
5) M. Chérest and H. Felkin, *Tetrahedron Lett.*, **1968**, 2205.
6) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
7) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).
8) G. E. Heinsohn and E. C. Ashby, *J. Org. Chem.*, **38**, 4232 (1973).
9) M. Muraki and T. Mukaiyama, *Chem. Lett.*, **1975**, 875.
10) E. J. Eisenbraun, *Org. Synth.* Coll. Vol. V, 310 (1973).
11) W. P. Neumann, *Ann. Chem.*, **667**, 1 (1963).
12) a) B. P. Dailey and J. N. Shoolery, *J. Am. Chem. Soc.*, **77**, 3977 (1955); b) B. Brownstein, B. C. Smith, G. Ehrlich, and A. E. Laubengayer, *ibid.*, **81**, 3826 (1959); c) J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1099 (1961).
13) H. B. Hetzer, R. G. Bates, and R. A. Robinson, *J. Phys. Chem.*, **67**, 1124 (1963).
14) H. H. Stroh und G. Westphal, *Chem. Ber.*, **96**, 184 (1963).
15) In most cases when more than 20% of *cis* alcohol was produced in the reaction of 4*t*BC with the TIBA–amine system, 10—80% of the unreacted 4*t*BC remained: reaction at a low temperature, result at an early stage of the reaction, reduction with TIBA–diethylamine or TIBA–aniline, and so on.