Asymmetric Reduction of Functionalized Ketones with a Sodium Borohydride–(L)-Tartaric Acid System

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The sodium borohydride–(L)-tartaric acid system is effective for the asymmetric reduction of prochiral ketones if they are functionalized on the α- or β-carbon with a group that can chelate to the chirally modified borohydride.

Chiral functionalized alcohols such as hydroxy esters are very important synthetic intermediates and much effort has been expended on developing a practical reduction system to obtain them from prochiral ketones.[1] Sodium borohydride ($NaBH_4$) is well known as a mild and highly selective reducing agent,[2] but the asymmetrically modified $NaBH_4$ system has been little examined in the reduction of functionalized ketones. We investigated chiral auxiliaries of $NaBH_4$, and found that (L)-tartaric acid was specifically very effective for the asymmetric reduction of α- or β-functionalized ketones. Yamazaki and his co-workers had already attempted the reduction of propiophenone using a $NaBH_4$–(D)-tartaric acid system in dioxane, but obtained only a low optical yield.[3] We now report a successful asymmetric reduction of functionalized ketones with a $NaBH_4$–(L)-tartaric acid system.

As shown in Table 1, the $NaBH_4$–(L)-tartaric acid system appeared to be low in its reactivity to simple ketones (Runs 1,2,3), and their products were almost racemic. On the other hand, the introduction of a functional group on the α-carbon of acetophenone raised the enantiomeric excess in the reduction of

those substrates in the order of Cl < OH < OMe. In the case of α-methoxyacetophenone, the optical yield was raised to 84 % e.e. (Run 7). These effects of the functional groups suggest that their affinities to a sodium or boron atom enable the ketones to chelate to the reductant,[8] and to facilitate the hydride-transfer and enantiomeric face selection by chirally modified $NaBH_4$.

This system was found to be effective for the reduction of keto esters which were expected to chelate to a reductant with their carbonyl and alkoxycarbonyl groups. Table 2 shows the results for keto esters.

Ethyl phenylglyoxylate was reduced to (*R*)-ethyl manderate in 86 % e.e. (Run 9). A keto carboxylic acid (Run 12), a keto carboxylic amide (Run 11), and a keto lactone (Run 14) were also able to be asymmetrically reduced to the corresponding hydroxylic products. Not only α-keto esters but also β-keto esters were reduced to the corresponding hydroxy esters in high optical yields. Thus, ethyl 2-oxopropionate (Run 6) and ethyl 3-oxobutanoate (Run 11) were readily and stereoselectively converted into the corresponding hydroxy esters (74 % e.e. and 81 % e.e., respectively). However, ethyl 4-oxopentanoate was reduced very slowly and the product was racemic (Run 18). From this fact, the weak co-ordination of the γ-keto ester, ethyl 4-oxopentanoate, to a reductant would lower its reactivity and the enantiomeric face selection by the reductant.

The ageing of the reagent, although used routinely to ensure complete removal of naked $NaBH_4$, only gave a slight improvement in asymmetric induction (Runs 9 *vs.* 10, 18 *vs.* 19).

As mentioned above, a functional group on the α- or β-carbon of the carbonyl group enables selective asymmetric induction in the $NaBH_4$–(L)-tartaric acid system. This finding bears uncanny parallelism to the Sharpless oxidation where a hydroxy group enables the asymmetric oxidation.[20] Since not only this system can be used under mild condition, but also both $NaBH_4$ and (L)-tartaric acid are so inexpensive, it is expected to be applied for the large scale operation in industries.

Table 1. Asymmetric reduction of ketones.*

Run	Ketones	Temp. (°C)	Time (h)	Yield[a] (%)	(*R*)/(*S*)	% E.e.
1	$CH_3(CH_2)_5COMe$	0	23	75[b]	52.0/48.0	4[4]
2	PhCOEt	R.t.	120	9[c]	50.0/50.0	0[5]
3	PhCOMe	R.t.	120	28[d]	49.9/50.1	0.2[6]
4	$PhCOCH_2Cl$	0	22	82	59.5/40.5	19[7]
5	$PhCOCH_2OH$	0	20	80	74.0/26.0	48[8]
6	$PhCOCH_2OMe$	0	19	95	(89.0/11.0)[e]	78
7	$PhCOCH_2OMe$	−20	69	87	(92.0/8.0)[e]	84

* Solvent = THF. The mixture of $NaBH_4$ and (L)-tartaric acid in THF was aged for 4 h under reflux. [a] Isolated yields. [b] Conversion = 85%. [c] Conversion = 20%. [d] Conversion = 48% [e] Analysis of the (+)-α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA ester). Their stereochemistries were not confirmed.

Experimental

Typical Procedure.—(L)-Tartaric acid was used (0.75–1.0 mol equiv.) to $NaBH_4$. Sodium borohydride was used 4 mol equiv. to a ketone. After addition of (L)-tartaric acid to the stirred suspension of $NaBH_4$ in tetrahydrofuran (THF), the mixture was stirred under reflux for 4 h. The mixture was cooled (0 to −20 °C) and then the solution of a ketone in THF was added to it with stirring. After the completion of reduction, 1M HCl was added to the mixture, and the resulting mixture was stirred for 15 min. Evaporation of THF was followed by extraction of the residue with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate and brine, and dried ($MgSO_4$). The crude product was purified by means of column chromatography on silica gel. The optical yields of products were determined by the optical rotation of the corresponding chiral products, or by ^1H NMR of their MTPA esters.

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Table 2. Asymmetric reduction of keto esters.*

Run	Keto Esters	Temp. (°C)	Time (h)	Yield[a] (%)	(*R*)/(*S*)	% E.e.
8	$PhCOCO_2Me$	−20	17	91	85.5/14.5	71[10]
9	$PhCOCO_2Et$	−20	19	87	93.0/7.0	86[11]
10[b]	$PhCOCO_2Et$	−20	24	85	92.5/7.5	85
11	$PhCOCONHCH_2Ph$	0	20	100	84.0/16.0	68[12]
12	$PhCOCO_2H$	0	67	93[c]	82.5/17.5	65
13	$MeCOCO_2Et$	−20	20	36	87.0/13.0	74[13]
14	$-C(Me)_2CH_2OCO-$	0	21	65	68.5/31.5	37[14]
15	$PhCOCH_2CO_2Et$	R.t.	96	20[d]	45.5/54.5	9[15]
16	$EtCOCH_2CO_2Et$	−20	23	83	87.5/12.5	75[16]
17	$MeCOCH_2CO_2Et$	0	21	73	84.0/16.0	68[17]
18	$MeCOCH_2CO_2Et$	−20	17	65	90.5/9.5	81
19[b]	$MeCOCH_2CO_2Et$	−20	13	59	89.5/10.5	79
20	$MeCOCH_2CO_2Bu$	−20	24	89	90.5/9.5	81[18]
21	$MeCOCH_2CO_2Bu^t$	−20	24	73	92.0/8.0	84[18]
22	$MeCOCH_2CONHPh$	−20	20	83	82.5/17.5	65[12]
23	$MeCOC(Me)_2CO_2Et$	−20	22	67	(80.0/20.0)[e]	60
24	$ClCH_2COCH_2CO_2Et$	−20	25	81	82.5/17.5	65[18]
25	$MeCO(CH_2)_2CO_2Et$	0	22	16[f]	50.0/50.0	0[19]

* Solvent = THF. The mixture of $NaBH_4$ and (L)-tartaric acid in THF was aged for 4 h under reflux. [a] Isolated yields [b] Without aging of the reductant [c] The product was converted into the methyl ester with diazomethane. [d] Conversion = 20%. [e] Analysis of the MTPA ester. Its stereochemistry was not confirmed. [f] Conversion = 66%.

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Paper 0/01189D
Received 22*nd January* 1990
Accepted 19*th March* 1990