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5(N-Methylbenzoylamino)-2, 2, 6, 6-tetramethylheptan-3-ol as a New Class of Recoverable Chiral Auxiliary

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Abstract: Reduction of α -ketoesters bearing 5(N-methylbenzoylamino)-2, 2, 6, 6-tetramethylheptan-3ol as a chiral auxiliary proceeds with high diastereoselectivity by using DIBAL as a reducing agent. The chiral auxiliary is recovered upon treatment with base, and α -hydroxy carboxylic acids are obtained in good chemical yields with high enantioselectivity.

We previously developed a 2, 2, 6, 6-tetramethyl-3,5-heptanediol (TMHDiol) derivative 1 as a new class of chiral auxiliaries.¹ This chiral auxiliary is an acyclic, but strongly conformationally biased, molecule. Conjugate addition of lithium N-benzyl-N-(trimethylsilyl)amide to the enoates bearing TMHD auxiliary proceeded with high diastereoselectivities to give β -amino esters in high yields.¹ Organocopper conjugate addition to TMHD enoates produced high diastereoselectivities,¹ and Diels-Alder reaction of TMHD acrylate with cyclopentadiene in the presence of TiCl₄ afforded an endo adduct exclusively with high diastereoselectivity.^{1,2}



 X=O, 5(benzoyloxy)-2,2,6,6-tetramethylheptan-3-ol TMHDiol derivative
X=NH, 5(benzolyamino)-2,2,6,6-tetramethylheptan-3-ol
X=NMe, 5(N-methylbenzolyamino)-2,2,6,6-tetramethylheptan-3-ol

Only the problem in the reactions of TMHDiol derivatives was that the chiral auxiliary could not be recovered; for example, conjugate addition of organocopper reagents to the enoates bearing 5(benzoyloxy) 2, 2, 6, 6-tetramethylheptane-3-ol chiral auxiliary produced the corresponding diesters 4, and the hydrolysis of 4 gave a mixture of benzoic acid, TMHDiol, and the desired conjugate adduct (carboxylic acid). It occurred to us that, if amide chiral auxiliaries such as 2 and 3 are utilized instead of 1, the ester group may be hydrolyzed selectively without destroying the amide bond and thus the chiral auxiliary may be recovered. We wish to report that in fact 3 acts as a recoverable chiral auxiliary.



We first studied the reduction of ketoesters bearing 1 and 2 as a chiral auxiliary. Synthesis of the benzoylamino auxiliary 2 is shown in Scheme 1. Pivaladehyde was converted to the corresponding oxime 5. Treatment of 5 with 3.3-dimethyl-1-butene/CH₂Cl₂/Et₃N/aqueous sodium hypochlorite solution gave isoxazoline 6 in 67% yield.³ Reduction with LiAlH₄ afforded the corresponding syn-amino alcohol 7 in 72% yield.⁴ Treatment of 7 with 1 eq benzoyl chloride in the presence of Et₃N gave 2 (racemic) in 84% yield.⁵ Ketoesters (8 or 9) were prepared by the reaction of RCOCOCI with either 1 or 2, respectively, in the presence of pyridine.



Scheme 1. Synthesis of 2 (racemic).



Table 1. Reduction of 8 and 9

entry	8 or	9	Reducing Agent	diastereomer	10 or 11
	<u></u>	<u>X</u>		ratio	yield, %
1	Me	0	DIBAL (1.2 eq)	60 : 40	45
2	Ph	0	DIBAL (1.2 eq)	70:30	41
3	Me	0	L-Selectride (1.0 eq)	64 : 36	57
4	Me	0	$LiAl(OtBu)_{3}H(1.2 eq)$	53 : 47	70
5	Me	0	DIBAL $(1.2 \text{ eq}) / \text{ZnCl}_2 (1.5 \text{ eq})$	94:6	78
6	Me	0	DIBAL $(1.2 \text{ eq}) / \text{MgBr}_2 \circ \text{OEt}_2 (1.5 \text{ eq})$	89:11	88
7	Ph	0	DIBAL $(1.2 \text{ eq}) / \text{ZnCl}_2 (1.5 \text{ eq})$	93 : 7	78
8	Ph	0	L-Selectride (1.0) / ZnCl ₂ $(1.5 eq)$	76 : 24	85
9	Ph	NH	DIBAL (1.2 eq)	50 : 50	89
10	Ph	NH	DIBAL $(1.2 \text{ eq}) / \text{ZnCl}_2 (1.5 \text{ eq})$	60 : 40	60

Reduction of 8 and 9 with DIBAL, L-Selectride, and LiAlH(OtBu)₃ is summarized in Table 1.

Reduction of 8 without an additive gave low diastereoselectivities (entries 1-3). In the presence of chelating agents such as $ZnCl_2$ and $MgBr_2 \cdot OEt_2$, reduction of 8 proceeded with high diastereoselectivities in good yields (entries 5-7). However, reduction of 9 produced very low diastereoselectivities regardless of the presence or absence of $ZnCl_2$ (entries 9-10). Highly diastereoselective reduction of 8 using DIBAL / $ZnCl_2$ is presumably due to chelating effect of $ZnCl_2$ as shown in 12. On the other hand, low diastereoselectivity via 9 may be ascribed to hydrogen bonding between NH and ester oxygen atom (13), which puts benzoyl group far away from acyl group and therefore the blocking effect of the aromatic ring is lost.



Accordingly, N-methylbenzoylamine auxiliary **3** was synthesized to avoid an unfavorable hydrogen bonding. Treatment of **7** with 0.5 equiv trichloromethylchloroformate / 2 equiv iPr_2NEt gave the cyclic carbamate **14** in 98% yield. Reduction with LiAlH₄ produced **15** in 92% yield.⁶ The usual benzoylation afforded **3** (racemic) in 88% yield. The corresponding ketoesters **16** were prepared by the reaction of RCOCOCl with **3** in the presence of pyridine in CH₂Cl₂; **16a** was obtained in 82% yield, **16b** in 87% yield, and **16c** in 96% yield. The reduction of **16a** with 1.2 equiv DIBAL gave an 80 : 20 diastereomer mixture of **17a** in 67% yield. The reduction of **16b** afforded an 88: 12 isomeric mixture of **17b** in 65% yield, and that of **16c** produced a 94 : 6 mixture of **17c** in 66% yield. As expected, removal of the effect of hydrogen bonding enhanced diastereoselectivity of reduction of **16a** with DIBAL / ZnCl₂ gave a 67 : 33 diastereomer mixture of **17a**. A reason for this ineffectiveness of the chelating agent is not clear.



Since high to good diastereoselectivity was obtained via 3 (racemic), we next investigated reduction using optically active 3 and tested recovery of the chiral auxiliary. Treatment of 3 (racemic) with (R)-5-oxo-2-tetrahydrofurancarboxylic acid⁷ in the presence of DCC / DMAP⁸ gave a diastereomeric mixture of 18 in

83% yield.⁹ Two diastereomers were separated by HPLC using YMC D-SIL-5-06 column; **18a** with 18.7 min retention time and **18b** with 20.1 min retention time. Hydrolysis of **18a** with KOH / EtOH-H₂O gave **3** (non-racemic); $[\alpha]^{26}$ +48.8° (C 0.94, CHCl₃). No epimerization took place in this hydrolysis step. Absolute configuration of (+)-**3** was determined as such from X-ray analysis of **18a**.



Optical active ketoester (+)-19 was synthesized by the standard method. Reduction of (+)-19 with DIBAL gave a 94 : 6 mixture of the corresponding hydroxy ester in 79% yield. Subsequent hydrolysis afforded (+)-3 in 93% yield and (S)-(+) mandelic acid in 98% yield. No epimerization of the recovered (+)-3 was observed. Since (S)-(+)mandelic acid was obtained, the reduction of (+)-19 would proceed as shown in 20.



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