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Asymmetric Aldol and Alkylation Reactions Mediated by the "Quat" Chiral Auxiliary (*R*)-(-)-5-Methyl-3,3-Dimethyl-2-Pyrrolidinone

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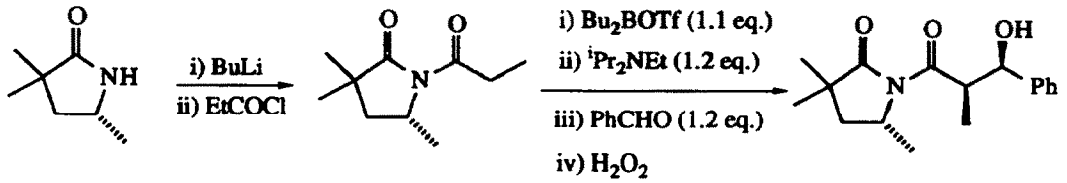
Abstract: Enolates derived from the *N*-propionoyl derivative of the "quat" chiral auxiliary (*R*)-(-)-5-methyl-3,3-dimethyl-2-pyrrolidinone undergo highly stereoselective aldol and alkylation reactions. Removal of the auxiliary has been demonstrated with LiOH, $PhCH_2OLi$, MeOMgBr and $LiAlH_4$ to generate respectively (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid in homochiral form, and with 96% e.e. (*S*)-2-methyl-3-phenylpropionic acid and derived methyl and benzyl esters and with >94% e.e. (*S*)-2-methyl-3-phenylpropanol.

In a preceeding communication[1] we have reported a synthetic route to the homochiral 5-substituted-3,3-dimethyl-2-pyrrolidinones, "quat" chiral auxiliaries, and demonstrated that the steric effect of the gem-dimethyl group is beneficial for increasing selectivity in the cleavage of their *N*-acyl derivatives using LiOH as the nucleophile. We demonstrate here examples of the synthetic utility of these quat chiral auxiliaries by reporting highly stereoselective aldol and alkylation reactions of enolates derived from the *N*-propionoyl derivative of (*R*)-(-)-5-methyl-3,3-dimethyl-2-pyrrolidinone **1**.

Treatment of the "quat" chiral auxiliary (*R*)-(-)-5-methyl-3,3-dimethyl-2-pyrrolidinone **1** with butyllithium followed by propionoyl chloride generated the *N*-propionoyl derivative **2** in 90% yield. Using the dibutylboron methodology developed by Evans[2], the *syn* aldol product **3** was obtained as a single diastereoisomer (>97% d.e.) by 300MHz NMR spectroscopy (Scheme 1).



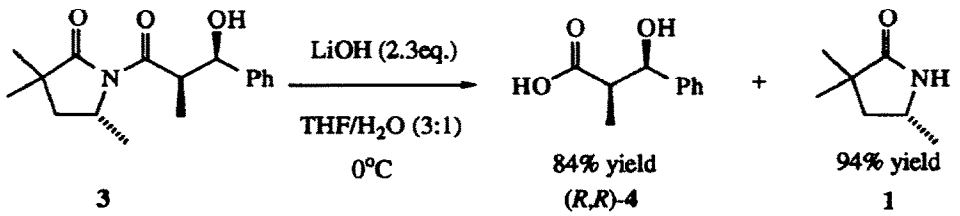
1 **2** **3**

Yield 84%; d.e. >97%

Scheme 1

In a representative procedure, a methylene chloride solution of the *N*-propionoyl pyrrolidinone **2**, at 0°C under an argon atmosphere, was treated successively with a 1.0M solution of dibutylboron triflate (1.1eq.) in methylene chloride, and then diisopropylethylamine (1.2eq.). To the resulting solution cooled to -78°C was added benzaldehyde (1.2eq.) and this mixture was stirred for 1 h at -78°C and 1.5 h at 0°C. The

reaction was then quenched by addition of pH 7 phosphate buffer solution and methanol, and treated with methanolic hydrogen peroxide at 0°C for 1 h. Analysis of the crude product mixture by 300 MHz ^{1}H NMR spectroscopy indicated the presence of only one diastereoisomeric product **3** (d.e. > 97%). The non crystalline adduct **3** was purified by flash column chromatography on silica gel. The *syn* relative stereochemistry of the aldol product was assigned on the basis of ^{1}H NMR coupling constants[3]. The coupling constant H_2-H_3 measured for the product **3** was 3.0Hz, consistent with the expected *syn* relative stereochemistry. The absolute configurations of the new stereogenic centres in **3** were assigned after removal of the chiral auxiliary. Hydrolysis of **3** using LiOH in a 3:1 mixture of tetrahydrofuran and water at 0°C generated 3-hydroxy-2-methyl-3-phenylpropionic acid **4** as a single diastereoisomer in 94% yield. Comparison of the specific rotation {$[\alpha]_D^{21}$ = +26.8 (c 0.5, CH_2Cl_2)} of the crystalline 3-hydroxy-2-methyl-3-phenylpropionic acid **4** thus obtained, with the literature value[2] for (2*S*,3*S*)-**4** {$[\alpha]_D^{22}$ = -26.4 (c 1.04, CH_2Cl_2)} established its absolute configuration as (2*R*,3*R*), (Scheme 2). The quat chiral auxiliary **1** was recovered nearly quantitatively in this hydrolysis with no products from endocyclic cleavage being observed.



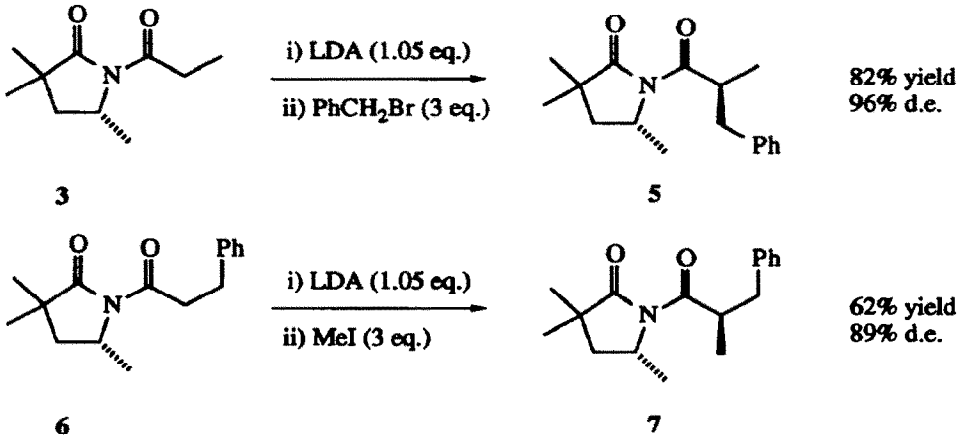
3 — 84% yield (*R*,*R*)-**4** — 94% yield **1**

Scheme 2

We next turned our attention to enolate alkylation reactions.[4,5] The lithium enolate of the *N*-propionoyl derivative **2** was formed in THF by addition at 0°C of lithium diisopropylamide LDA (1.05eq. solution in THF). After 1 h at 0°C an excess (3eq.) of benzyl bromide was added. The reaction was quenched by addition of pH 7 phosphate buffer solution and the crude product **5** extracted with diethyl ether. The diastereomeric excess of the crude alkylated product was determined as 96% by 300 MHz ^{1}H NMR spectroscopic analysis (Scheme 3) with the relative configurations being assigned after hydrolytic removal of the auxiliary, as described below. Quenching the lithium enolate derived from the corresponding 3-phenylpropionoyl derivative **6** with methyl iodide generated the complementary diastereoisomer **7** with a diastereoisomeric excess of 89% (Scheme 3). The yields of purified diastereoisomers **5** and **7** were 82% and 62% respectively. The yields and diastereoselectivities for these alkylation reactions are comparable with those reported by Evans *et al* using lithium enolates derived from 4-substituted oxazolidin-2-ones.[4,5]

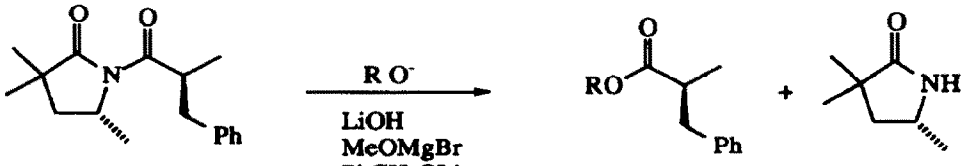
The non crystalline products were purified by flash column chromatography on silica gel. Unfortunately, the separation of the diastereoisomers formed could not be achieved. The lower yield observed for the formation of **7** can be explained by a slower alkylation with methyl iodide and the instability of the lithium enolate at 0°C, which decomposes *via* a ketene pathway. As for the aldol products, the absolute configuration of the new stereogenic centres in **5** and **6** could be assigned by comparison of the

specific rotation of the products obtained after hydrolytic or reductive removal of the auxiliary with literature values.



Scheme 3

Treatment of diastereoisomer **5** (96% d.e.)with LiOH, MeOMgBr, and $PhCH_2OLi$ gave rise to (*S*)-2-methyl-3-phenylpropionic acid **8** and the corresponding methyl ester **9** and benzyl ester **10** respectively.

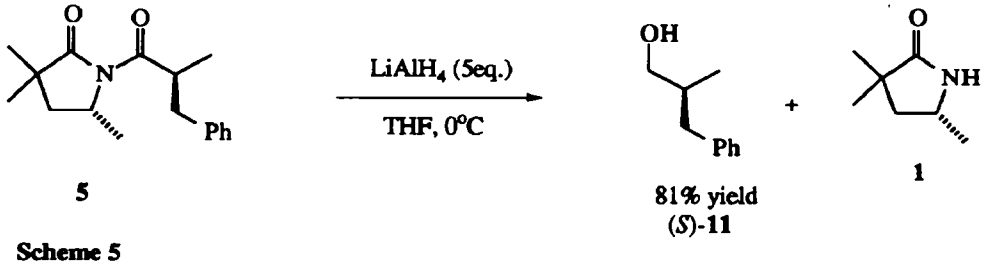


Product	R	Yield	e.e.	$[\alpha]_D^{21}$	Yield of 1
8	H	83%	96%	+28.6 (c 1.0, $CHCl_3$)	95%
9	Me	82%	96%	+34.5 (c 0.8, $CHCl_3$)	92%
10	$PhCH_2$	94%	96%	+25.7 (c 1.15, $CHCl_3$)	97%

Scheme 4

^1H NMR spectroscopic analysis of each of the crude products **8-10** from these different reactions indicated in each case the total absence of endocyclic cleavage. The absolute configurations (*S*) and enantiomeric purity of products **8-10** were determined by comparison of their specific rotations with the literature values and/or by ^1H NMR spectroscopic analysis using chiral shift reagents [6]. No significant racemisation occurred during these cleavage reactions.

Finally treatment of **5** (96% d.e.) with an excess of $LiAlH_4$ in THF at 0°C furnished in 84% yield the alcohol (*S*)-**11** (>94% e.e.) $[\alpha]_D^{20} = -10.3$ (c 0.9, benzene), lit.[7] $[\alpha]_D^{24} = -11$ (c 4.6, benzene) and the auxiliary **1** in practically quantitative yield.



5

81% yield
(*S*)-**11**

1

Scheme 5

In conclusion the results presented in this communication show the "quat" chiral auxiliary (*R*)-(-)-5-methyl-3,3-dimethyl-2-pyrrolidinone **1** to be a very effective chiral auxiliary in asymmetric alkylations and aldol reactions. In particular the reactions to remove the chiral auxiliary from the elaborated substrate occur very efficiently allowing effective recovery of the "quat" chiral auxiliary.

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References and notes

1 See preceeding communication.

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