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Chiral Synthesis of 3-Substituted and 3,3-Disubstituted γ-Butyrolactones by Enantioselective Deprotonation Strategy

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Abstract: Chiral synthesis of 3-substituted and 3,3-disubstituted γ-butyrolactones was achieved by employing an enantioselective deprotonation of the corresponding cyclobutanone derivatives with chiral bases as a key reaction.

Enantioselective deprotonation of meso or prochiral compounds using chiral lithium amide bases provides useful chiral intermediates for the synthesis of a wide variety of organic compounds including natural products.[1] Recently we have applied this methodology to the enantioselective preparation of 4,4-disubstituted cyclohexanones aimed at the construction of a chiral quaternary carbon center, and have succeeded in the synthesis of (+)-α-cuparenone.[2] In the course of our continuing work on enantioselective deprotonation of cycloalkanones, we have been interested in the development of a novel synthetic path to chiral substituted γ-butyrolactones, since compounds having such a ring system are often observed in nature and also are biologically significant.

The strategy which we have developed, involves an enantioselective deprotonation of cyclobutanone derivatives, followed by oxidative bond cleavage of the resulting silyl enol ethers. (Figure 1)

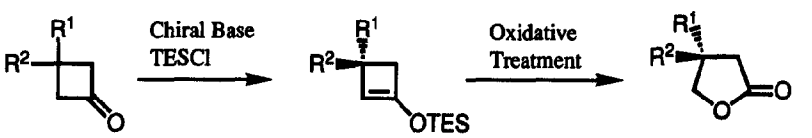
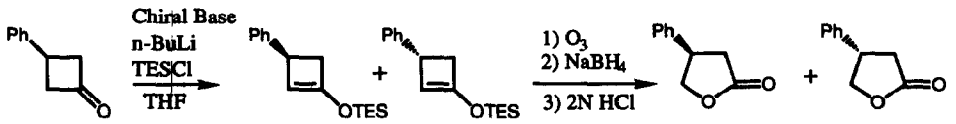


Figure 1

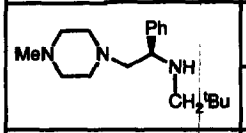
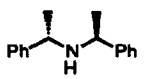
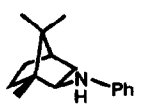
We first attempted an enantioselective deprotonation reaction of 3-phenylcyclobutanone (**1**),[3] since no systematic investigation on an asymmetric induction for four membered cycloalkanones with chiral lithium amide bases seems to have been described. Thus, the treatment of **1** with lithium (*R*)-2-(4-methylpiperazin-1-yl)-*N*-neopentyl-1-phenylethylamide in tetrahydrofuran and 1.0 equiv. of hexamethylphosphoric triamide (HMPA) at -78°C in the presence of triethylsilyl chloride (TESCl) afforded the silyl enol ether (**2**) in 74% yield. Whereas, none of the desired silyl enol ether (**2**) could be isolated with the use of trimethylsilyl chloride (TMSCl) in this reaction, probably because of its instability. The enantiomeric excess of the product, after its

conversion to the known lactone (**3**) by ozonolysis and subsequent reductive work-up with sodium borohydride, was determined to be 45% e.e. and the absolute configuration was also confirmed by comparison of its optical rotation with that of the literature.[4] When this reaction was carried out with lithium (*S*, *S'*)-α, α'-dimethyldibenzylamide at -100°C, the enantioselectivity was increased to 92% e.e. in 67% conversion yield. Results for the enantioselective deprotonations of **1** using other chiral bases are listed in the Table 1, which indicates that the chiral base having C_2 symmetry seems to be superior to the other bases for asymmetric induction of 3-mono-substituted cyclobutanone derivative.

Table 1. Enantioselective Deprotonation of 3-Substituted Cyclobutanone with Chiral Bases



1 (*S*)-**2** (*R*)-**2** (*R*)-**3** (*S*)-**3**

Chiral Base	Solv.	Temp.(°C)	Silyl Enol Ether (**2**)		Lactone (**3**)			
			Yield (%)	$[\alpha]_D$ [a]	Yield (%)	$[\alpha]_D$ [a]	Configuration	e.e. (%)[b]
	THF - HMPA [c]	-78	74	-1.8	78	+23.3	S	45
	THF - HMPA [c]	-100	68	-1.9	73	+24.2	S	47
	THF	-78	67	-3.1	75	+39.9	S	77
	THF	-100	67	-3.7	70	+47.6	S	92
	THF	-78	70	+0.5	73	-6.5	R	13

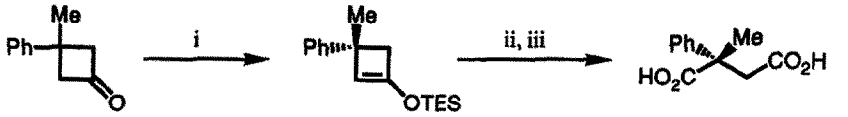
a) Measured in $CHCl_3$ at 25 ± 1°C

b) Determined by comparison with reported $[\alpha]_D$ value.

c) 1.0 equiv. of HMPA was used.

Having obtained satisfactory results in enantioselective deprotonation of a 3-substituted cyclobutanone derivative, we next examined the synthesis of 3,3-disubstituted γ-butyrolactone by application of the above strategy using 3-methyl-3-phenylcyclobutanone (**4**), prepared according to the literature,[5] as a starting material. Based on the consideration of the above results, enantioselective deprotonation of **4**, followed by *in situ* trapping of the enolate with triethylsilyl chloride, was attempted by employing lithium (*S*, *S'*)-α, α'-dimethyldibenzylamide as the chiral base at -78°C. However, the enantiomeric excess of the product was only 12% based on the HPLC analysis using the chiral column, CHIRALCEL OJ (Daicel Chemical Industries, Ltd.). When this reaction was carried out with lithium (*R*)-2-(4-methylpiperazin-1-yl)-*N*-neopentyl-1-phenylethylamide in tetrahydrofuran at -78°C, its enantiomeric excess was increased to 51%. Furthermore,

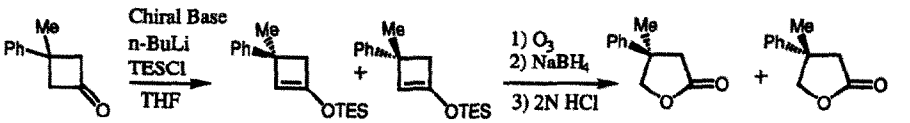
improved enantioselectivity (78% e.e.) was obtained with the use of 1.0 equiv. of HMPA as a co-solvent in either tetrahydrofuran or toluene as a solvent at -100°C. The results obtained are summarized in the Table 2.



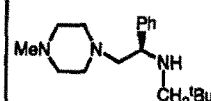
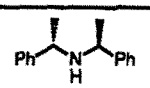
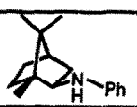
i) lithium (*R*)-2-(4-methylpiperazin-1-yl)-*N*-neopentyl-1-phenylethylamide, TESCl, THF-HMPA, -78°C; ii) O_3, MeOH, -78°C; iii) H_2O_2-HCO_2H, -40 to -10°C.

Scheme 1

Table 2. Enantioselective Deprotonation of 3,3-Disubstituted Cyclobutanone with Chiral Bases



4 (*S*)-5 (*R*)-5 (*R*)-6 (*S*)-6

Chiral Base	Solv.	Temp.(°C)	Silyl Enol Ether (5)		Lactone (6)			
			Yield (%)	$[\alpha]_D$ [a]	Yield (%)	$[\alpha]_D$ [a]	Configuration	e.e. (%)[b]
	THF - HMPA [c]	-78	70	+42.5	73	+12.5	S	72
	THF	-78	71	+30.1	70	+8.8	S	51
	Tol - HMPA[c]	-78	70	+43.2	72	+12.7	S	73
	THF - HMPA [c]	-100	68	+46.3	72	+13.6	S	78
	THF	-100	65	+35.5	70	+10.5	S	60
	THF	-78	85	+6.9	75	+2.1	S	12
	THF	-78	74	-4.3	68	-1.3	R	7

a) Measured in $CHCl_3$ at 25 ± 1°C

b) Determined based on HPLC analysis using the chiral column CHIRALCEL OJ (Daicel Chemical Industries, Ltd.).

c) 1.0 equiv. of HMPA was used.

The absolute configuration of 3-methyl-3-phenyl-γ-butyrolactone (**6**) was determined by conversion of (*R*)-(+)-**5** into (*S*)-(-)-2-methyl-2-phenylsuccinic acid, $[\alpha]_D$ -14.4 (EtOH) {lit.,[6,7] $[\alpha]_D$ -20.1(EtOH)} by ozonolysis and subsequent oxidative treatment with hydrogen peroxide,[8] as shown in Scheme 1.

Thus, we have established a novel synthetic route to 3-substituted and 3,3-disubstituted γ-butyrolactones by means of enantioselective deprotonation of cyclobutanone derivatives and we are currently investigating the synthesis of natural products by application of this strategy.

References and Note

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