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ASYMMETRIC ACYLATION OF CARBOXAMIDES HAVING trans-2,5-BIS(METHOXYMETHOXYMETHYL)PYRROLIDINE MOIETY AS A CHIRAL AUXILIARY AND STEREOSELECTIVE REDUCTION OF THE RESULTING 2-ALKYL-3-OXO AMIDES

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Summary: trans-2,5-Bis(methoxymethoxymethyl)pyrrolidine proved to be an excellent chiral auxiliary for the asymmetric acylation of the corresponding carboxamide enolates and the stereoselective $Zn(BH_4)_2$ reduction of the resulting 2-alkyl-3-oxo amides provided a useful alternative to asymmetric aldol reaction.

Recently, we reported[1] a general and highly stereoselective reduction of 2-alkyl-3-oxo amides with $Zn(BH_4)_2$.[2] Here, we describe the introduction of chirality to the method as its useful extension, by combining it with a new asymmetric acylation. Chiral trans-2,5-bis-(methoxymethoxymethyl)pyrrolidine which proved to be an excellent chiral auxiliary for the alkylation of amide enolates,[3] has successfully been used in the acylation, giving a hitherto not attained high selectivity of 98% de in most cases.[4] Quite recently, Evans et al.[5] have reported a similar asymmetric acylation of chiral oxazolidone imide enolates with de's up to 92%, and syn-reduction of the products with $Zn(BH_4)_2$.

Results of the present asymmetric acylation (**1**→**2**) and the subsequent reduction (**2**→**3**) are listed in the Table.

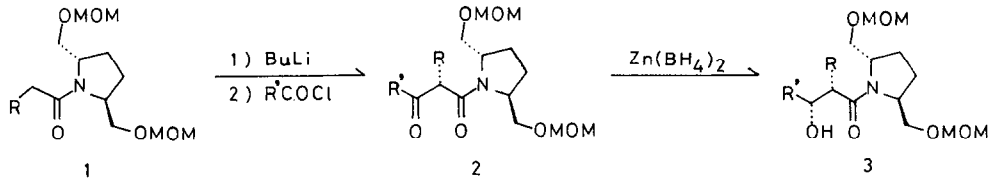
Acylation of the propionamide (**1**) with α-substituted acyl chlorides proceeded with high chemical yields (entries 2, 3, 4, 5, 6, 11, and 12). On the other hand, satisfactory yields were obtained with acyl chlorides not branched at α-carbon atom or with benzoyl chloride only when the solution of the amide enolate was added at -78°C to the solutions of acyl chlorides in THF (entries 1, 7, 8, 9, and 10). α,β-Unsaturated acid chlorides gave poor yields (<25%) by usual procedure, but the addition of $ZnCl_2$ (1.2 equiv.) to the amide enolate solutions before acylation improved the yields to a considerable extent (entries 13 and 14). In all cases, however, stereoselectivity of the acylation was excellent. The acylated products (**2**) could be isolated by neutral work-up without any detectable epimerization. Examination of the stereochemistry at the acylated carbon atom revealed that the acylation occurred in the same sense as the alkylation previously reported[3] (entries 1, 2, 3, 4, 8, and 9; ref. b of the Table).

Isolated acylation products could be reduced by $Zn(BH_4)_2$ in the same way as described in the previous report[1] to the corresponding syn-2-alkyl-3-hydroxy amides (**3**) with high selectivity. In one-pot experiment without the isolation of acylated products (entries 3, 6, and 9), a reduced stereoselectivity (syn:anti=2:1~9:1) was observed when a solution of $Zn(BH_4)_2$ was added to the acylated mixture, but by the addition of the acylated mixture to the $Zn(BH_4)_2$ solution, satisfactorily high selectivity was obtained. The effect of lithium ion which causes low stereoselective reduction may be suppressed by the reverse addition.

A typical example of acylation is given below.

n-BuLi (1.80 mol dm^{-3}, 73 μl, 1.05 eq) was added slowly to the THF (0.5 ml) solution of (2S,5S)-N-propionyl-2,5-bis(methoxymethoxymethyl)pyrrolidine (35.0 mg) at -78 C under nitrogen.

After stirring for 10 min at -78 °C, the solution was added to a solution of benzoyl chloride (15.5 µl, 1.05 eq) in THF (0.1 ml). Then the solution was poured on sodium phosphate buffer (pH 7). Extraction (CH_2Cl_2), washing, drying, concentration and TLC on silica gel gave (2S,5S,2'S)-N-(2'-methyl-3'-oxo-3'-phenylpropionyl)-2,5-bis(methoxymethoxymethyl)pyrrolidine (43.0 mg, 90%).



1 2 3

Table. Asymmetric Acylation Using (2S,5S)-1 and Subsequent Stereoselective Reduction with Zinc Borohydride in THF at -78 °C

Entry	R'in R'COCl	R in 1	Acylation Product(2)		Reduction Product(3)[c]	
			yield(%)	% de[a)b)]	yield(%)	syn:anti[a)]
1	C_2H_5	CH_3	74	98	96	99:1
2	$(CH_3)_2CH$	CH_3	95	98	99	>99:1
3[d)]	$(CH_3)_2CH$	CH_3			50	99:1
4[e)]	$(CH_3)_2CH$	CH_3	89	96		
5	$(CH_3)_3C$	CH_3	80	98	99	96:4
6[d)]	$(CH_3)_3C$	CH_3			94	91:9
7	C_9H_{19}	CH_3	90	98	98	>97:3[f)]
8	Ph	CH_3	90	98	93	>99:1
9[d)]	Ph	CH_3			85	>99:1
10	$PhCH_2$	CH_3	76	98	98	99:1
11	$(CH_3)_2CH$	C_2H_5	88	98	98	>99:1
12	$(CH_3)_2CH$	$PhCH_2$	96	98	98	99:1
13[g)]	$CH_3CH=CH^t$	CH_3	47	98	97	97:3[h)]
14[g)]	$PhCH=CH^t$	CH_3	61	98	95	>99:1[h)]

a) Diastereomeric ratios were determined from intensities of relevant ^{1}H-NMR signals. b) Configurations were determined to be (2'S) by optical rotation of hydrolyzed products (entries 1~4) or by comparing ^{1}H-NMR signals with authentic samples after hydrogenolysis of 3'-hydroxyl group (entries 8 and 9). Other products were not determined. c) All the new compounds gave satistactory NMR and elementary analyses. d) Reduction was carried out without the isolation of acylated product. e) Acylation was conducted at 0 °C. f) Determined by ^{13}C-NMR. No peaks of the other diastereomer were detected. g) Zinc enolate prepared by adding $ZnCl_2$ solution (1 mol dm^{-3}) in THF to the Li enolate, was added to the acid chloride solution in THF at -20 °C, and stirred for 10 min. h) Ratio was determined after successive hydrogenation (H_2/PtO_2), hydrolysis, esterificaton (CH_2N_2) and acetylation (Ac_2O, 4-dimethylaminopyridine).

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