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ORGANOALUMINUM REAGENT AS A CHEMICAL TOOL FOR ASYMMETRIZATION

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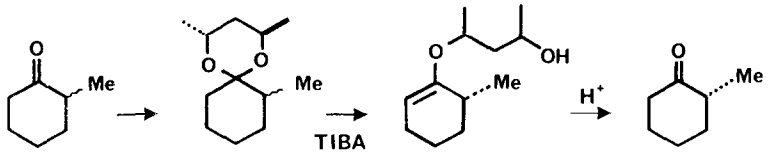
Summary: A new process is described for the asymmetrization of meso ketones using organoaluminum reagent.

Enzymes have a remarkable ability to recognize the stereochemical properties of chiral or prochiral substrate and catalyze chemical transformations with a high degree of stereospecificity. From the synthetic point of view, the most spectacular application of these unique properties are the asymmetrization of the symmetric diester with pig liver esterase and its application to the synthesis of antibiotics by Ohno.[1] Can asymmetrization of the similar type be observed in a purely nonbiochemical reaction?[2] This paper addresses an approach which heavily depends on organoaluminum reagents and homochiral protecting group.[3]

Our initial concern was to find the direct method for the conversion of a meso ketone to an asymmetric enolate using chiral lithium amides.[4,5] However, difficulties were soon encountered in the synthesis of chiral amines of an appropriate structural features. Meanwhile, the chiral acetal approach as an effective asymmetric synthesis have been developed by our group[6] and others[7] which certainly must be the logical extension of this work. Furthermore, the successful selective kinetic resolution of cyclic ketones (Scheme 1) recently

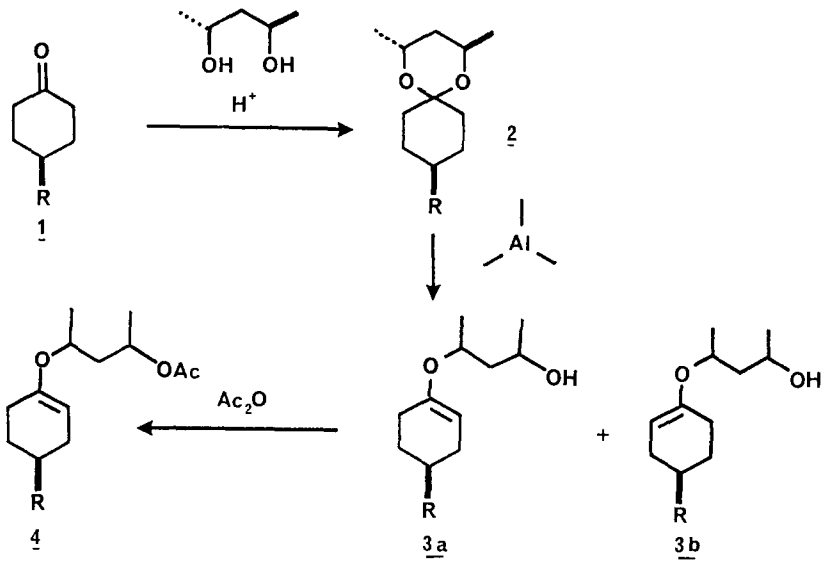
SCHEME 1



+ Recovered Acetal

developed by us provided an additional stimulus.[8] We describe herein a new synthetic method based on these considerations with organoaluminum reagent. The method appears to offer special advantages of efficiency of the reaction and more importantly procedural simplicity. Two modifications have been studied, one involving triisobutylaluminum and the other dialkylaluminum amides,[9] as expressed by scheme 2.

SCHEME 2



Treatment of the meso ketone **1** (R = Me) with (2R,4R)-2,4-pentanediol in the presence of pyridinium tosylate produced the acetal **2** (R = Me) in >95% yields. It was subjected to excess triisobutylaluminum in dichloromethane at -78°C for 30 min and 0°C for 4 h to give the enol ether **3** (R = Me), which was directly converted to the corresponding acetate **4**. Gc analysis of the product revealed the diastereoratio of 9 : 1. The absolute configuration of the ether was determined as S by an independent synthesis.[10] The results of several experiments with a variety of substrates are summarized in Table 1.

Although the practicality of the triisobutylaluminum method is apparent, further studies are necessary to increase the stereoselectivities of the reaction. The ideal reagent for this type of elimination reaction appeared to be dialkylaluminum amides previously developed by us for the oxirane rearrangement.[9] Thus, we have synthesized a variety of aluminum amides to test the selectivities of the reaction. Most of these were either totally ineffective as reagents or less satisfactory than triisobutylaluminum. However, it was finally ascertained that the amide **6** performed the desired

transformations with superior reactivity and selectivity to the triisobutylaluminum method. Table 2 summarized the results.

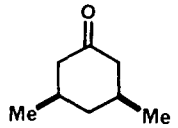
Table 1. Asymmetrization of cyclic ketones using triisobutylaluminum

Entry	Acetal	Reaction Conditions			Yield	Ratio
		equiv	Solvent	Temp(°C),h	(%)	**3a : 3b**
1	**2**, R = Me	4	CH_2Cl_2	0, 4	99	87 : 13[10]
2		4	CH_2ClCH_2Cl	0, 6	90	77 : 23
3		4	Toluene	0, 6	53	76 : 24
4		4	Hexane	0, 6	37	84 : 16
5		4	$CHCl_3$	0, 5	58	84 : 16
6		10	CH_2Cl_2	0, 6	76	88 : 12
7		20	CH_2Cl_2	-20, 9	70	88 : 12
8		20	CH_2Cl_2	-40, 5	72	88 : 12
9		4	CH_2Cl_2	-78, 0.5; 0, 8	99	90 : 10
10	**2**, R = Et	4	CH_2Cl_2	-78, 0.5; 0, 8	99	86 : 14
11	**2**, R = ^{t}Bu	4	CH_2Cl_2	-78, 0.5; 0, 8	99	89 : 11[11]
12	**5**	4	CH_2Cl_2	-78, 0.5; 0, 8	99	91 : 9

Table 2. Asymmetrization of cyclic ketones using dialkylaluminum amides

Entry	Acetal	Reagent(equiv)	Solvent	Temp(°C),h	Yield	Ratio
					(%)	**3a : 3b**
1	**2**, R = Me	Me_2AlTMP[a] (4)	Toluene	0, 2	16	82 : 18
2		Et_2AlTMP (4)	Toluene	0, 6	90	84 : 16
3		$^iBu_2AlTMP$ (4)	Toluene	0, 10	70	81 : 19
4		**6**[12] (4)	Toluene	0, 4	99	89 : 11
5		**6** (10)	Toluene	-78, 0.5; 0, 6	48	90 : 10
6		**7**[12] (4)	Toluene	0, 8	<5	-- : --
7	**2**, R = Et	**6** (10)	Toluene	-78, 0.5; 0, 6	91	92 : 8
8	**2**, R = ^{t}Bu	**6** (10)	Toluene	-78, 0.5; 0, 6	95	88 : 12
9	**5**	**6** (10)	Toluene	-78, 0.5; 0, 6	69	94 : 6

[a] TMP = 2,2,6,6-Tetramethylpiperidide



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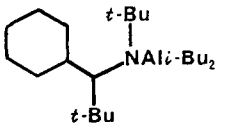
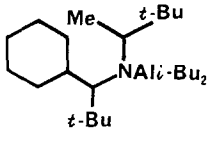


6[12]



7[12]

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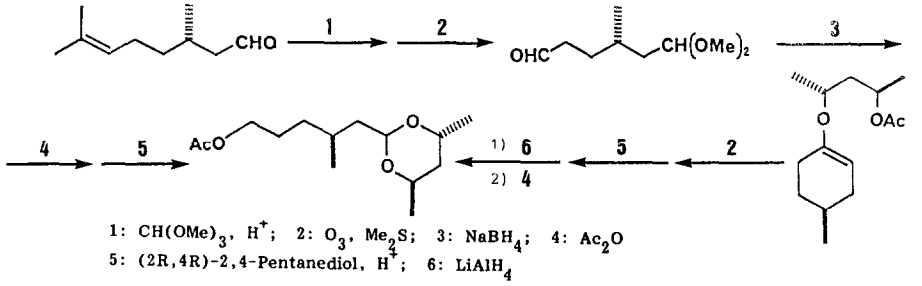

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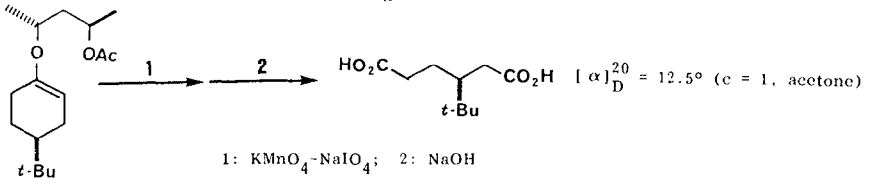

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