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ASYMMETRIC PINACOL-TYPE REARRANGEMENT OF α-HYDROXY METHANESULFONATES PROMOTED BY TRIETHYLALUMINUM —— PREPARATION OF OPTICALLY PURE α-ARYL AND α-VINYL KETONES ——

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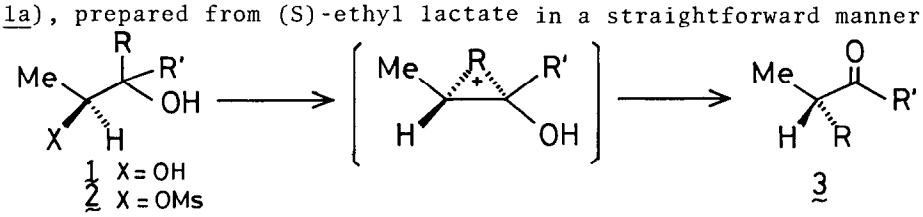
Summary: Asymmetric (stereospecific) pinacol-type rearrangement of aryl or vinyl group in α-hydroxy methanesulfonates is promoted by Et_3Al in CH_2Cl_2 at -78°C to afford optically pure α-aryl or α-vinyl ketones.

Pinacol rearrangement is a fundamental process in organic chemistry and one of the powerful methods for the synthesis of ketones.[1] However, the scope of the reaction is severely limited so long as the chirality problems are concerned; involvement of a free carbocation rather than a concerted process leads to a loss of stereospecificity. For instance, treatment of (R)-2-amino-1,1-diphenyl-1-propanol with nitrous acid gave (R)-1,2-diphenyl-1-propanone with 24 % racemization.[2] To our knowledge, any of the conditions that ensure the fully concerted nature of this type of reaction (especially in acyclic case) have not established so far. Thus, asymmetric (stereospecific) pinacol-type rearrangement has been left aside despite its conceptual simplicity and potential utility. Recently, we disclosed a stereospecific thermal 1,2-rearrangement of aryl groups leading to optically active 2-arylalkanoic acids.[3] Prompted by this observation and synthetic potential of the reaction, we envisioned the development of the stereospecific pinacol-type rearrangement of optically active 1,2-diols leading to the chiral ketones. In this letter, we wish to report a novel and extremely facile pinacol-type rearrangement of α-hydroxy methanesulfonate (α-hydroxy mesylate) promoted by triethylaluminum to afford optically pure α-aryl or α-vinyl ketones.

First stage of our reaction is the regioselective sulfonylation of sec-tert vicinal diol, which posed little problem. (S)-1,1-Diphenyl-1,2-propanediol (1a), prepared from (S)-ethyl lactate in a straightforward manner, was



1 X = OH
2 X = OMs

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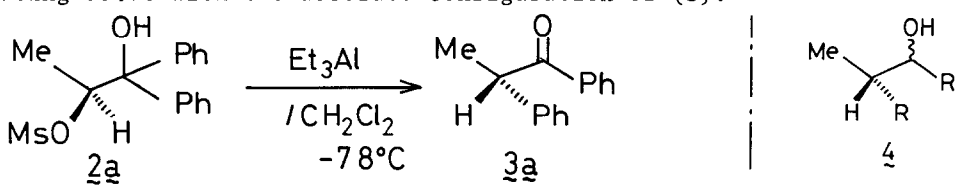
treated with CH_3SO_2Cl (1.2 eq) - Et_3N (1.5 eq) in CH_2Cl_2 at 0°C to afford the α-hydroxy mesylate 2a (R=R'=Ph) in 87% yield. The regioselectivity at this stage was confirmed to be over 95% by ^1H NMR.

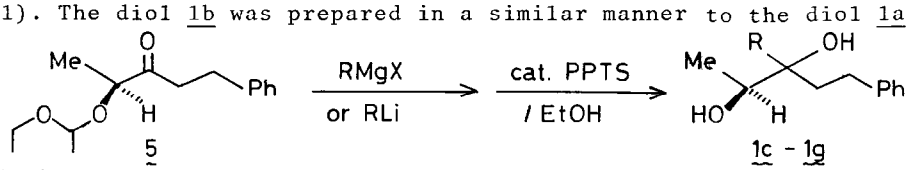
Next, the chiral α-hydroxy mesylate 2a, thus prepared, was subjected to various conditions to effect the rearrangement. While thermal reactions failed,[4] Et_3Al was found to be an excellent promoter in the present reaction; the α-hydroxy mesylate 2a was smoothly converted to the rearranged ketone 3a within 5 min at -78°C in CH_2Cl_2 by the action of 1.2 eq Et_3Al.

The mode of the migration of the phenyl group was proved to be stereospecific with an inversion of the preexisting chiral center: After the rearrangement, the ketone 3a was directly reduced with diisobutylaluminum hydride (DIBAL) (1.5 eq, -78°C, 15 min) to give 1,2-diphenyl-1-propanol (4a) as a 5/1 mixture of diastereomers, which was converted to the corresponding (+)-MTPA esters.[5] An authentic sample of racemic 4a was also prepared according to the same procedure starting from racemic ethyl lactate, and converted to the (+)-MTPA esters. HPLC and ^{19}F NMR analysis of these samples indicated that the ee of the chiral center in question is over 99 %. The $[\alpha]_D$ value of 3a was +200° indicating 99%ee with the absolute configuration of (S).[6]



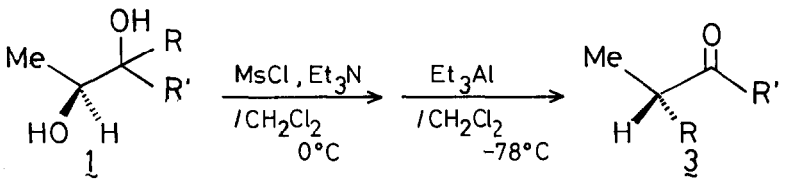
A typical procedure for the rearrangement of (S)-2-methanesulfonyloxy-1,1-diphenyl-1-propanol (2a) is described: Under an argon atmosphere, a hexane solution of Et_3Al (0.6 mmol, 0.7 ml) was slowly added to the α-hydroxy mesylate 2a (153 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) at -78°C. During the addition, the solution turned to yellow,[7] which was stirred for further 30 min, and quenched with 3 drops of pH 7 phosphate buffer. The resultant mossy suspension was diluted with AcOEt and dried with anhydrous Na_2SO_4, filtered through a Celite pad and concentrated. The oily residue was chromatographed on a Florisil column[8] to afford (S)-1,2-diphenyl-1-propanone (100 mg, 96 %) ($[\alpha]_D^{25}$ +200° (c 1.1, $CHCl_3$), lit. $[\alpha]_D^{23}$ +202°(c 3.5, $CHCl_3$)).[6]

In order to examine the feasibility of the present reaction, various chiral 1,2-diols were prepared from (S)-ethyl lactate and tested. The ketone 5, prepared via (S)-N,N-dimethyllactamide, was allowed to react with Grignard reagents or 2-furyllithium[9] to afford, after deprotection of ethoxyethyl group (cat. PPTS / EtOH; rt, 1hr),[10] the diols 1c-1g as diastereomeric pairs (ratio: 1/1 - 5/1). The diol 1b was prepared in a similar manner to the diol 1a.



These alcohols were regioselectively mesylated by the method described above and extractively worked up.[11] The crude α-hydroxy mesylates 2b-2g were subjected to the rearrangement to afford 3b-3g. The ee value of each product was determined by HPLC and/or ^{19}F NMR study of (+)-MTPA esters of 4b-4g which were obtained by DIBAL reduction of 3b-3g, respectively (vide supra).

TABLE I. Asymmetric Pinacol-Type Rearrangement [15]



Entry	Diol	R	R'	Yield(%)[a]	ee(%)	$[\alpha]_D$(c, temp.)[d]
1	1a	C_6H_5-	C_6H_5-	83	>99[b,c]	+200°(1.1, 25)
2	1b	p-$CH_3C_6H_4$-	p-$CH_3C_6H_4$-	77	>99[b,c]	+122°(0.74, 27)
3	1c	C_6H_5-	$C_6H_5(CH_2)_2$-	86	>99[b,c]	+138°(0.42, 29)
4	1d	p-$CH_3C_6H_4$-	$C_6H_5(CH_2)_2$-	79	>99[b,c]	+136°(0.92, 29)
5	1e	p-$CH_3OC_6H_4$-	$C_6H_5(CH_2)_2$-	96	>99[b,c]	+141°(0.80, 26)
6	1f	H_2C=CH-	$C_6H_5(CH_2)_2$-	75	>99[c,e,f]	+135°(0.34, 27)
7	1g		$C_6H_5(CH_2)_2$-	75	>95[b,f]	+ 45°(0.50, 27)

a) Overall yield from 1, after purification by column chromatography on Florisil (see note 8). b) Determined by 19-F NMR analysis of (+)-MTPA esters of alcohols 4. c) Determined by HPLC analysis of (+)-MTPA esters of alcohols 4 ——— Develosil ODS-5 column (MeOH-H_2O). d) Measured in $CHCl_3$. e) See note 18). f) Rearrangement was performed at -42°C.

As shown in the table, this Et_3Al-promoted two-step sequence is effective for a variety of chiral diols, and the corresponding chiral ketones[12] of high enantiomeric purities were obtained in good yields. The level of the activation of α-hydroxy mesylates is high enough to permit vinyl[13] or 2-furyl group to participate in the migration. It is also noteworthy that, due to the mild reaction conditions, a chiral α-vinyl ketone was obtained without contamination of the corresponding conjugated ketone. The present reaction offers a novel and facile entry into α-aryl or α-vinyl ketones which are hardly accessible by the asymmetric alkylation of chiral enolate derivatives.[14]

The present reaction could be regarded as a ligand exchange reaction on aluminum. We assume a cyclic intermediate as depicted in figure I where the hard-hard interaction between Al-MsO groups[16] and the pushing effect of the aluminum alkoxide[17] ensure the concerted nature of the present process to effect the complete chirality transfer. It is also worthy of comment that the ambivalent nature of Et_3Al nicely fits in the reaction —— i) an activator of mesyloxy group as a Lewis acid, and ii) an acid captor.

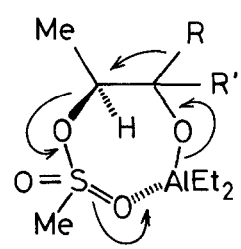


Fig. I

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6) F. A. A. Elhafez and D. J. Cram, J. Am. Chem. Soc., 74, 5846 (1952).

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8) Purification on silica-gel plate caused a partial racemization (~10 %).

9) V. Ramanathan and R. Levine, J. Org. Chem., 27, 1216 (1962).

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12) The products which resulted from the migration of $C_6H_5(CH_2)_2$- group could not be detected, which showed that the migration of aryl, vinyl, or 2-furyl group took place exclusively.

13) Recently, Wender et al. reported a similar approach, reductive rearrangement of alkynyl halohydrins. However, the stereochemical feature of the reaction has not been clarified: P. A. Wender, D. A. Holt, and S. M. Sieburth, J. Am. Chem. Soc., 105, 3348 (1983).

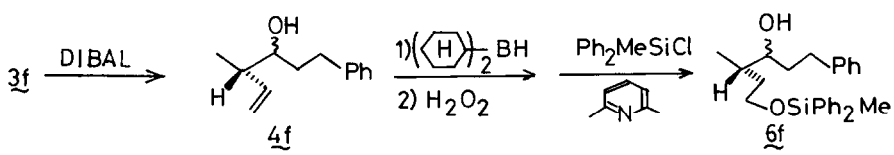
14) For example; D. Enders and H. Eichenauer, Chem. Ber., 112, 2933 (1979).

15) All new compounds exhibited satisfactory ^1H NMR, IR, and MS properties.

16) Activation of sulfonates by organoaluminum compounds and its efficient use in the Beckmann rearrangement; see K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, J. Am. Chem. Soc., 105, 2831 (1983).

17) Formation of aluminum alkoxide at -78°C; see H. Fujii, I. Tsukuma, T. Saegusa, and J. Furukawa, Makromol. Chem., 82, 32 (1965).

18) Enantiomeric excess of 3f was estimated as follows; 3f was first converted to the mono-silylated alcohols 6f, both in chiral and racemic forms, whose (+)-MTPA esters were subjected to HPLC analysis.



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