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AUXILIARY STRUCTURE AND ASYMMETRIC INDUCTION IN THE "MUKAIYAMA-ALDOL" REACTIONS OF CHIRAL SILYL KETENE ACETALS.

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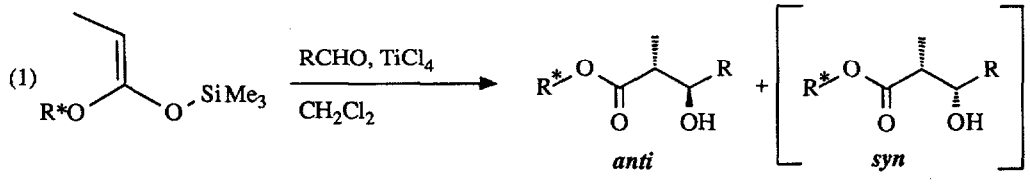
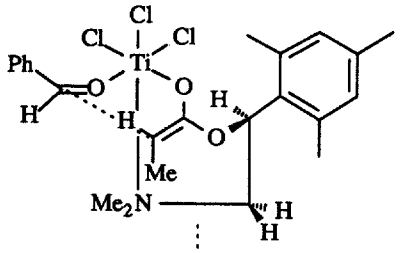
*Abstract.- A variety of chiral auxiliaries R*OH were prepared and tested for levels of asymmetric induction control in the "Mukaiyama-aldol" reaction of chiral silyl ketene acetals. Structural features required for high levels of control are discussed.*

In 1985 we reported a new method for the control of absolute stereochemistry using the "Mukaiyama-aldol" reactions of chiral silyl ketene acetals derived from N-methylephedrine (Eq.1).[1] This methodology was successfully applied to the enantioselective synthesis of *anti* α-methyl-β-hydroxyesters (e.e.91-94%),[1,2,3] α-methyl-β-alkoxyaldehydes (e.e.91%),[4] α-hydrazino and α-aminoacids (e.e.78-91%),[5] α-methyl-δ-oxoesters (e.e.72-75%),[3] *cis* and *trans* β-lactams (e.e.70-96%),[6,7] carbapenem antibiotics,[8,9] and other natural products.[10,11] In this paper we report on the influence that the nature of the chiral auxiliary (R*) has on the stereoselectivity and discuss the mechanism of the diastereofacial differentiation process.



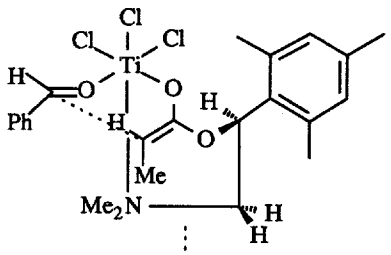
Anti-syn* ratios.** The *anti-syn* ratios reflect the combined π-facial selectivities of the silyl ketene acetal and of the aldehyde. While the enolate π-facial selectivity can be very high (e.g. entry 8, Table; **1**:**3** >99:1 ; **2**:**4** >99:1 ; **1**+**2**:**3**+**4** >99:1), the aldehyde π-facial selectivity is usually moderate (e.g. entry 8; **1**:**2** 77:23), and the *anti-syn* ratios reflect this mediocre selectivity. Furthermore, while the enolate π-facial selectivity can somehow be controlled by the size and the stereoelectronic properties of the chiral auxiliary R* (vide infra), the aldehyde π-facial selectivity cannot be controlled, and probably depends on which of the two carbonyl oxygen lone pairs is coordinated to titanium, the energy difference between the two complexes being relatively small.[12] Pictorial models of the hypothetical transition structures leading to the *anti1**:*syn***2** mixture of entry 8 are shown in Figure 1.

Silyl ketene acetal π-facial selectivity. As N-methylephedrine has two stereocenters (1S,2R or 1R,2S), it is interesting to know which of the two is responsible for the asymmetric induction and the absolute configuration of the reaction products. Entries 1-4 of the Table answer this question. Stereocenter 1 is responsible for the overall sense of the asymmetric induction while stereocenter 2 has a minor cooperative effect



1 (anti) 77%

Figure 1



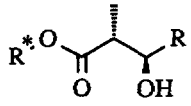
2 (syn) 23%

in the 1S,2R case (N-methylephedrine, entries 1,2) and a minor negative effect in the 1S,2S case (N-methyl-ψ-ephedrine, entry 3), or can even be removed without significant stereochemical consequences (entry 4).

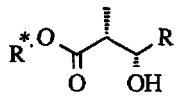
The role of various substituents at C-1 was then investigated (entries 4-9); apparently the enolate π-facial selectivity seems to depend on the different steric requirements of the substituents which can be inferred from their conformational A values:[13] Me 1.70, C_6H_{11} 2.15, C_6H_5 3.0. A comparison of the "small" methyl with the "bulky" cyclohexyl group (entries 5,7) reveals that steric effects play an important role in the control of reaction stereoselectivity. Although it is difficult to unequivocally dissect noncovalent electronic interactions from the accompanying steric effects which together define reaction stereoselectivity, a comparison of the results of the aliphatic (entries 5-7) with those of the aromatic substituents (entries 1-4, 8-9) clearly shows that the aromatic moiety of the auxiliary is critically important for high levels of asymmetric induction. The aromatic ring is presumably intimately involved at the transition state with the titanium ion to which the aldehyde and the enolate are complexed. Although we cannot conclude from our results precisely how the aromatic group of these chiral auxiliaries influences asymmetric induction, it is clear that some property of the aromatic ring, be it size, shape or electronic character, is essential for high stereoselectivity.[14]

By comparing entries 1,2 with 4,5,6 and 8,9 some other interesting observations can be made: a) as in other reactions involving diastereofacial differentiation processes[15,16,17] the fully saturated cyclohexyl group gives worse results compared to the corresponding aromatic b) aromatic aldehydes give better selectivities than aliphatic c) when no aromatic group is present either in the auxiliary or in the aldehyde (entry 6), no stereoselectivity is observed.

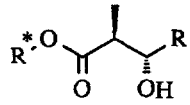
Synthesis of the Auxiliaries and Reaction Procedures. (1S,2R) N-methylephedrine $[\alpha]_D^{20}$+30°(c 4.5, MeOH)(entries 1,2) is commercially available (Fluka). (1S,2S) N-methyl-ψ-ephedrine $[\alpha]_D^{20}$+38.7°(c 6.65, MeOH) (entry 3) was synthesized (H_2CO, HCO_2H, reflux) from commercially available (1S,2S) ψ-ephedrine (Fluka). The (S) phenyl derivative $[\alpha]_D^{20}$+74.1° (c 1.29, $CHCl_3$)(entry 4) was synthesized from (S) mandelic acid *via* the following route: AcCl;[18] $SOCl_2$; Me_2NH; LAH,THF,reflux. The (S) cyclohexyl derivative $[\alpha]_D^{20}$+37.5° (c 5.39, $CHCl_3$)(entries 5,6) was synthesized from (S) hexahydromandelic acid *via* the same route described above. The (S) methyl derivative $[\alpha]_D^{20}$+23.2° (c 0.9, EtOH)(entry 7) was synthesized from (S) ethyl



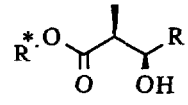
1



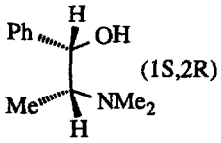
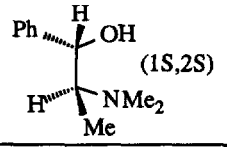
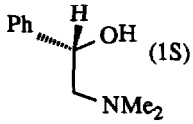
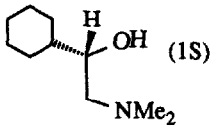
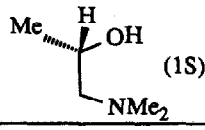
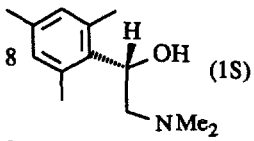
2



3



4

Table Entry	R*OH	RCHO	anti/syn (1+3/2+4)	anti1/anti3
1	 (1S,2R)	PhCHO	85:15	97:3
2		n-C_3H_7CHO	80:20	95.5:4.5
3	 (1S,2S)	PhCHO	77:23	93:7
4	 (1S)	PhCHO	63:37	95.5:4.5
5	 (1S)	PhCHO	87.5:12.5	90:10
6		n-C_3H_7CHO	92.1:7.9	44:56
7	 (1S)	PhCHO	83:17	40:60
8	 (1S)	PhCHO	77:23	>99:1
9		n-C_3H_7CHO	72:28	91.5:8.5

lactate *via* the following route: Me_2NH,MeOH,H_2O; LAH,THF,reflux. The (S) mesityl derivative $[\alpha]_D^{20}$+60.2° (c 1.0, MeOH)(entries 8,9) was synthesized from 2,4,6-trimethylacetophenone *via* the following route: Br_2,AcOH;[19] Me_2NH,benzene;[20] LAH,Et_2O; resolution by ester formation with (R) PhCHOMeCOCl, flash-chromatography (CH_2Cl_2-acetone 90:10) and saponification (NaOH,MeOH,H_2O).

Propionate synthesis (CH_3CH_2COCl, CH_2Cl_2), (E) silyl ketene acetal synthesis (LDA,THF,TMSCl), aldol condensation conditions ($TiCl_4$,CH_2Cl_2,-78°C) and aldol product stereochemistry analysis were essentially identical to those described in ref.3. Silyl ketene acetal yields were uniformly high (90-100%) with E/Z ratios ranging from 90:10 to >95:5. Condensation yields were usually high (tipically 80%) and were occasionally improved to >90% by the use of 4 A molecular sieves in the reaction mixture.[21]

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