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Origin of diastereoselectivity in the addition of allylsilane to chiral acyclic mixed acetals

Kavita Manju and Sanjay Trehan*

Department of Chemistry, Panjab University, Chandigarh-160 014, India. E-mail: strehan@panjabuniv.chd.nic.in

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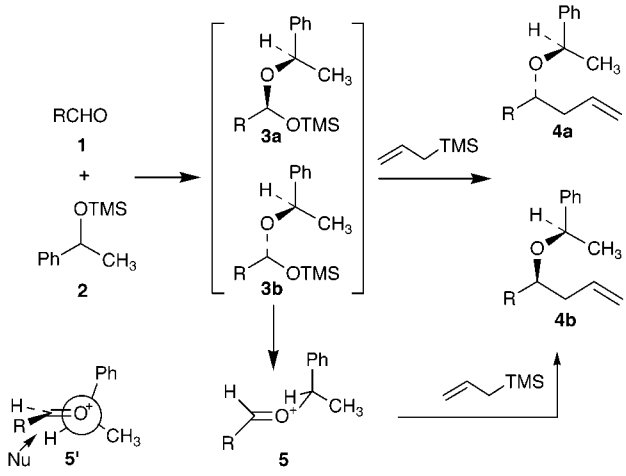
Addition of allylsilane to chiral acyclic mixed acetals has been found to proceed *via* an S_N1 mechanism and a model has been proposed to explain the observed diastereoselectivity.

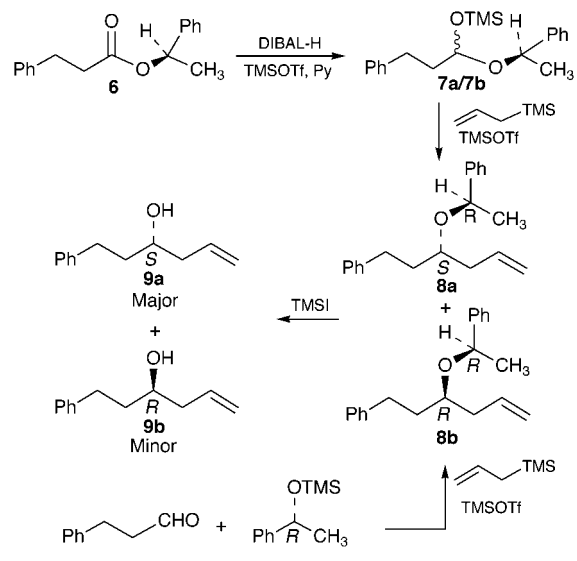
Over the last couple of decades great strides have been made in the Lewis acid catalysed reaction of chiral acetals with silyl nucleophiles. Chiral cyclic acetals have been studied in detail and the mechanism as well as the diastereofacial selectivity of their reaction is now well-established.[1] Despite the fact that chiral mixed acyclic acetals prepared *in situ* give homoallylic ethers in high diastereoselectivity,[2] an understanding of the origin of the diastereoselectivity is lacking. In order to comprehend the origin of the diastereoselectivity one needs to first establish the mechanism (S_N1 or S_N2) because there is support for both type of mechanisms in the literature.†[3] If the reaction proceeds *via* an S_N2 mechanism, then the origin of the diastereoselectivity should lie in the diastereoselective formation of a silyl acetal intermediate which would undergo allylation in a stereospecific manner (Scheme 1). In such a case the diastereomeric ratio of the silyl acetal (**3a**:**3b**) and homoallylic ether (**4a**:**4b**) should be the same. Alternatively, if the reaction proceeds *via* an S_N1 mechanism, a common oxocarbenium ion **5** will be formed from both the silyl acetal intermediates. The diastereoselectivity in this case will be determined by the extent of 1,3-induction[4] and will be independent of the ratio of the silyl acetals (**3a**:**3b**) (Scheme 1). Houk has proposed a theoretical model for the nucleophilic addition on this type of oxocarbenium ion by invoking a weak 1,3-allylic interaction and has shown reaction occurring from the most stable conformation **5′** giving **4b** as the major product.[5] Herein, we report our results which establish the mechanism and the diastereoselectivity of this reaction.

Chiral ester **6** prepared from (*R*)-1-phenethyl alcohol and hydrocinnamic acid was treated with 1 equiv. of DIBAL-H and the intermediate was treated with TMSOTf and pyridine[6] to give acetal **7a**/**7b** as a mixture of diastereomers in the ratio of 54:46 (Scheme 2).‡ This mixture of acetals was treated with 0.1 equiv. of TMSOTf and 1.5 equiv. of allyltrimethylsilane in toluene at −78 °C to give homoallylic ether **8a**/**8b** in 79% yield. The diastereomeric ratio was found to be 82:18 from its ^{1}H NMR, which was vastly different from its precursor acetals. Identical diastereoselectivity was also obtained when hydrocinnamaldehyde was treated with the trimethylsilyl ether of (*R*)-1-phenethyl alcohol and allyltrimethylsilane in the presence of TMSOTf in toluene at −78 °C. These two experiments suggests an S_N1 mechanism whether the mixed acetal is prepared *in situ* or is isolated before allylation.

The configuration of the newly created chiral centre was established to be *S* from the optical rotation of the corresponding homoallylic alcohol **9a**/**9b** {$[\alpha]_D$ −12.6 (*c* 1, $CHCl_3$); lit.[7] +16.9 (*c* 1, $CHCl_3$) for the *R* isomer with 80% ee} obtained by treatment of **8a**/**8b** with iodotrimethylsilane.[8] Thus the major diastereomer formed is (*S*,*R*)-**8a**, just as reported in earlier work,[2] and not (*R*,*R*)-**8b** as as identified mistakenly by Houk as the major product obtained by Mukaiyama[2b] and Seebach[2c] while applying his model.[5] Since the Houk model is not applicable to the system under investigation an alternate model is desirable. The reaction of the oxocarbenium ion intermediate is expected to be exothermic in nature, therefore in the absence of any polar group in the chiral centre, the ground state conformation of the oxocarbenium ion should be important in determining the diastereoselectivity.[9] In order to establish the importance of steric or stereoelectronic effects on the conformational preferences of the oxocarbenium ion intermediate leading to the product, various silyl ethers with R groups of increasing steric bulk were synthesised and used in the allylation reaction.[10] The results are summarised in Table 1. The configuration of the products was assigned as done earlier except when silyl ethers with isopropyl groups were used, because they could not be prepared in reasonable optical purity. In these cases the configuration was established by correlation of their ^{1}H NMR with that of **8**.

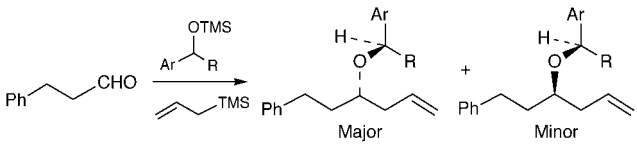


Scheme 1



Scheme 2

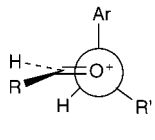
Table 1 Reaction of hydrocinnamaldehyde with various silyl ethers and allylsilane[ab]



Entry	Ar	R	Diastereomer ratio[c]	Yield (%)
1	Ph	Me	82:18 (4.5:1)	89
2	Ph	Et	85:15 (5.7:1)	82
3	Ph	Pr^i	86:14 (6.1:1)[d]	85
4	*o*-Tolyl	Me	88:12 (7.3:1)	82
5	*o*-Tolyl	Et	93:07 (13.3:1)	88
6	*o*-Tolyl	Pr^i	91:09 (10.1:1)[d]	80

[a] All reactions were carried out in toluene at −78 °C under nitrogen atmosphere. [b] Enantiomeric excess of silyl ethers used in entries 1, 2, 4 and 5 were 94, 89, 90 and 81% respectively (ref. 11) and (±)-silyl ethers were used in entries 3 and 6. [c] Diastereomeric ratio was determined *via* ^{1}H NMR. [d] Configuration was established by correlation of ^{1}H NMR with that of **8**.

If steric effects were important, then one would expect a decrease in diastereoselectivity with a decrease in the steric difference between the medium and large groups. However, the opposite trend was observed and generally diastereoselectivity increased as the size of the alkyl group increased in the two series studied (Table 1, entries 1–3 and 4–6). This suggests that stereoelectronic effects stabilise certain select conformations of the oxocarbenium ion leading to the product. In the absence of any electrostatic effects,[12] the important stereoelectronic interactions between the three groups of the chiral centre and the C=O bond which can restrict the conformational mobility of the chiral centre are σ*–π* and π–π* (hyperconjugation).[13,14] However, conformation **10** obtained using the σ*–π* interaction[10] is similar to Houk's model[5] and therefore does not appear to be important. Therefore hyperconjugation between the substituents of the chiral centre and the oxocarbenium ion appears to be the predominant stereoelectronic interaction.



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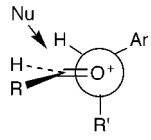
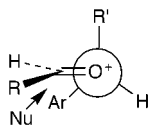
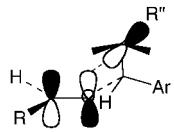


11a



11b



12

We suggest that the reaction proceeds through a conformation where the alkyl group occupies the *anti* position. In conformations **11a** and **11b** besides normal α–β C–C hyperconjugative stabilisation of the oxocarbenium ion there is an additional stabilisation due to bonding between the β–γ substituents, as depicted in **12**.[14c] This stabilisation is greater for a C–C bond than for a C–H bond.[14c] Therefore ethyl or isopropyl groups should stabilise conformations **11a** and **11b** more than a methyl group over other conformations. This additional stabilisation is missing for bonding between the chiral carbon and aryl groups or hydrogen.§¶‖

We conclude that C–C hyperconjugative stabilisation of the oxocarbenium ion restricts the conformation of the chiral centre to **11a** and **11b** leading to major and minor diastereomers. The observed diastereoselectivity is due to the differential interaction of the nucleophile with the hydrogen in **11a** and the aryl groups in **11b**. Accordingly higher diastereoselectivity is observed for the *o*-tolyl series.

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Notes and references

† Mukaiyama has proposed an S_N2 mechanism for the allylation of chiral mixed acyclic acetals [ref. 2(*b*)].

‡ No attempt was made to assign the configuration of the newly generated acetal chiral centre in the major and minor isomer.

§ Since C(sp^3)–C(sp^2) is a stronger bond therefore C(sp^3)–C(sp^2) hyperconjugation may not be as important as C(sp^3)–C(sp^3) hyperconjugation.

¶ The silyl ether of 1-deutero-1-phenylethyl alcohol gave product in an 86:14 ratio (compare Table 1, entry 1). The increase in diastereoselectivity indicates that the C–H or C–D bond stabilises the oxocabenium ion by inductive effects and not by hyperconjugation (ref. 15).

‖ Linderman has also invoked hyperconjugative stabilisation of the oxocarbenium ion intermediate by R_3Si in diastereoselective Mukaiyama-type aldol reactions of silyl-substituted mixed acyclic acetals (ref. 16). We thank one of the referees for bringing this reference to our notice.

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