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Acetate aldol reactions of chiral oxocarbenium ions

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Abstract—Chiral oxocarbenium ions have been exploited to carry out highly diastereoselective and enantioselective acetate aldol addition reactions. The chiral auxiliary has been optimized to give the product with good diastereoselectivity.

Aldol addition reactions have greatly influenced asymmetric carbon–carbon bond formation reactions and are one of the most powerful tools for constructing β-hydroxy carbonyl compounds.[1] Several diastereoselective and enantioselective aldol reactions have been developed and successfully applied for the synthesis of biologically important compounds.[2] Chiral auxiliary based aldol reactions are useful for the preparation of single isomers of β-hydroxy carbonyl derivatives and represent perhaps the most important breakthrough to date in this area.[3] However, most of the chiral auxiliaries that perform well in diastereoselective propionate aldol reactions often perform poorly in acetate aldol reactions with only a few exceptions.[4] Some chiral catalysts and indirect methods have also been developed to carry out acetate aldol reactions.[5] Oxocarbenium ions generated from chiral acyclic acetals bearing chiral auxiliaries have been investigated by various groups for the Hosomi–Sakurai reaction.[6] However, their utility in other reactions has not been explored in detail.[7] As part of our efforts to understand and optimize diastereoselective addition reactions in systems with weak 1,3-allylic strain,[8] we herein report an efficient method for carrying out highly diastereoselective and enantioselective acetate aldol addition reactions using chiral oxocarbenium ions.

A mixture of the trimethylsilyl ether of 1-phenylethyl alcohol **1** and hydrocinnamaldehyde **2** was treated with 1-trimethylsilyloxystyrene **3**, at −78 °C, in toluene using 10 mol % of trimethylsilyltrifluoromethanesulfonate (TMSOTf) as catalyst following Marko's protocol as used for allylation reactions.[9] To our disappointment, the product formed was not the expected β-alkoxy ketone **4** but the β-hydroxy ketone **5**, which was presumably formed by direct aldol reaction between silyl enol ether **3** and hydrocinnamaldehyde **2**.[10] This result indicated that the silyl enol ether **3** reacted preferentially with the aldehyde **2** to give aldol product **5** rather than with silyl ether **1** to give mixed acetal **6**, the expected precursor of **4**, presumably due to the higher reactivity of silyl enol ether **3** as compared to silyl ether **1** (Fig. 1).

From this result, we realized that in order to develop an oxocarbenium ion bearing a chiral auxiliary for enantiofacial addition of silyl enol ethers to give aldol products we needed to prepare mixed acetals before attempting the aldol reaction. To check this, the ester of 1-phenylethyl alcohol and hydrocinnamic acid **7** was treated with DIBAL-H at −78 °C and the resulting aluminate was treated in situ with TMSOTf and pyridine[11] at −78 °C to give mixed acetal **6** (Scheme 1), which was quickly passed through a short silica gel column, pretreated with 0.1% triethylamine in hexane. To our delight, treatment

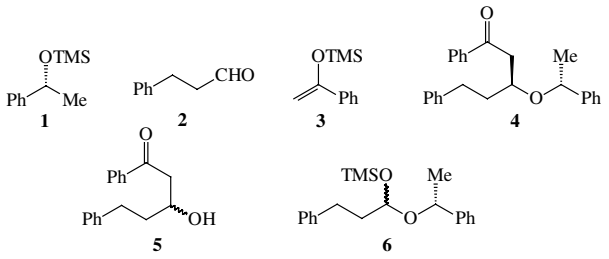

Figure 1.

Keywords: Acetate aldol reaction; Oxocarbenium ions; 1,3-Allylic strain; Diastereoselective; Enantioselective.
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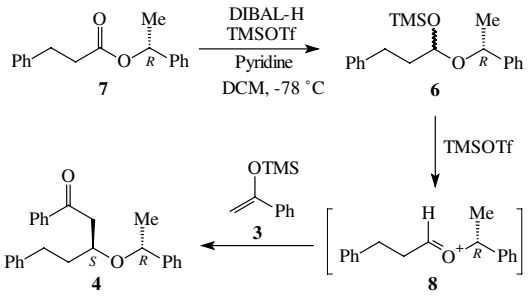


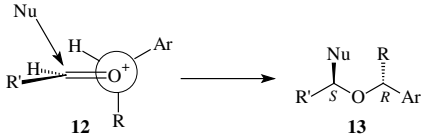
Scheme 1.

of mixed acetal **6** with 1-trimethylsilyloxy styrene **3** in the presence of 10 mol % of TMSOTf in CH_2Cl_2 at 0 °C gave the desired product **4** in 80% yield but with very poor diastereoselectivity (1.2:1). Changing the solvent to toluene improved the diastereoselectivity to 1.8:1, which was further improved to 2.7:1 when the reaction was carried out at −78 °C in toluene. Based on our previous studies on the Hosomi–Sakurai reaction,[8a] we investigated the effect on the diastereoselectivity of the product formed by substituting the phenyl group with a substituted phenyl group and changing the stereogenic methyl to higher homologues. The results are compiled in Table 1.

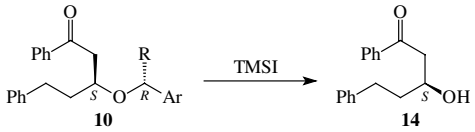
For the phenyl series (Ar = Ph) the diastereoselectivity increased on changing the alkyl group from methyl to ethyl and further to an isopropyl group (Table 1, entries 1–6). For the *o*-toluyl series (Ar = 2-CH_3–C_6H_4) the diastereoselectivity increased as the alkyl group was changed from methyl to ethyl. However, for R = *i*-Pr a decrease in the diastereoselectivity was observed (Table 1, entries 7–9). *ortho*-Substituted aryl groups gave better diastereoselectivity over *para*-substituted compounds (Table 1, compare entries 7 and 10 with 11 and 12). The best diastereoselectivity was obtained with the silyl acetal having Ar = 2-CH_3–C_6H_4 and R = Et.[12] The configuration of the major diastereomer in these reactions was assigned according to the model proposed by us for allylation reactions (Scheme 2).[8a]

In order to confirm further the configuration of the newly generated stereogenic center, compound **10** was treated with freshly prepared iodotrimethylsilane to give alcohol **14** (Scheme 3).[14] The configuration of **14** was determined to be *S* by comparing the optical rotation value $[\alpha]_D^{25}$ +17.1 (*c* 2.8, $CHCl_3$) with that of the literature[15] {$[\alpha]_D^{25}$ +10.0 (*c* 2.8, $CHCl_3$), for 50% optically pure product}, thus supporting our model for the prediction of diastereoselectivity involving oxocarbenium ions.[8a]

After optimizing the diastereoselectivity, aldol reactions with other substrates using silyloxystyrene **3** and ketene acetal **16** were investigated. The results are compiled in Table 2. The diastereoselectivity was consistently high for aliphatic substrates and was poor in the case of the aryl substrate investigated (Table 2, entry 4). The lower



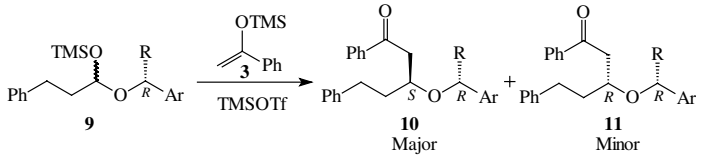
Scheme 2.



Ar = *o*-toluyl, R = Et

Scheme 3.

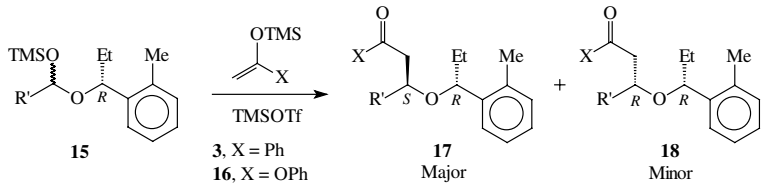
Table 1. Reaction of various mixed acetals **9** with silyl enol ether **3**[a]



Entry	Ar	R	Solvent	Diastereomeric ratio of β-alkoxy ketones **10**:**11**[b]	Isolated yield (%)
1	C_6H_5	Me	DCM	68:32	89
2	C_6H_5	Et	DCM	74:26	88
3	C_6H_5	*i*-Pr	DCM	82:18	86
4	C_6H_5	Me	Toluene	73:27	80
5	C_6H_5	Et	Toluene	84:16	83
6	C_6H_5	*i*-Pr	Toluene	93:7	79
7	2-CH_3–C_6H_4	Me	Toluene	83:17	80
8	**2-CH_3–C_6H_4**	**Et**	**Toluene**	**95:5**	**88**
9	2-CH_3–C_6H_4	*i*-Pr	Toluene	93:7	81
10	2-Cl–C_6H_4	Me	Toluene	82:18	80
11	4-CH_3–C_6H_4	Me	Toluene	71:29	80
12	4-Cl–C_6H_4	Me	Toluene	70:30	84

[a] All reactions were carried out at −78 °C under a nitrogen atmosphere.
[b] Diastereomeric ratio was determined by 300 MHz ^{1}H NMR analysis.

Table 2. Reaction of acetal **15** with enol ether **3** and ketene acetal **16**[a]



15 **3**, X = Ph; **16**, X = OPh **17** Major **18** Minor

Entry	R′	Nucleophile	Diastereomeric ratio of β-alkoxy ketones/esters[b] **17**:**18**	Isolated yield (%)
1	CH_3CH_2	**3**	96:4	89
2	CH_3	**3**	97:3	90
3	$PhCH_2$	**3**	91:9	84
4	Ph	**3**	60:40	74
5	$Ph(CH_2)_2$	**16**	91:9	90
6	CH_3CH_2	**16**	95:5	87
7	CH_3	**16**	98:2	86

[a] All reactions were carried out at −78 °C under a nitrogen atmosphere.
[b] Diastereomeric ratio was determined by 300 MHz ^{1}H NMR analysis.

diastereoselectivity observed for R = Ph is in tune with the results obtained for the Hosomi–Sakurai reaction,[6] which could be the result of *E*/*Z* isomerization of the oxocarbenium ion intermediate due to conjugation with the phenyl group.[16]

In conclusion, this study establishes that oxocarbenium ion intermediates can be exploited to carry out highly diastereoselective and enantioselective acetate aldol addition reactions in a predictable manner. This method can be used for the synthesis of complex molecules.

Acknowledgements

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was determined to be 95% from the ^{1}H NMR of the corresponding Mosher ester.[13b]

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