Diastereoselective aldol reactions with butane-2,3-diacetal protected glyceraldehyde derivatives

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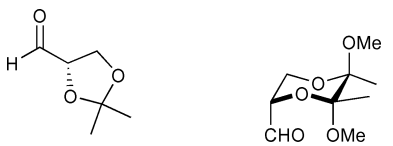
Diastereoselective aldol coupling reactions with butane-2,3-diacetal (BDA) protected glyceraldehyde derivatives are reported. Good selectivities of up to 20 : 1 for the homologated aldol products have been achieved in preparatively useful yields.

Owing to the prevalence of the 1,3-oxidation pattern found in polyketide natural products, the aldol reaction has become the principal carbon–carbon bond-forming process used in their synthesis.[1] Extensive development of enantioselective versions of this important reaction have led to significant advances in the use of auxiliaries and asymmetric catalysts.[2] In many studies of the aldol reaction (*S*)-glyceraldehyde acetonide **1** (and its enantiomer) has been used as a coupling partner (Fig. 1).[3] Yet despite its popularity as a three-carbon chiral building block this compound has some limitations; it is readily polymerised, easily racemised and has a propensity to form hydrates.[4] For these reasons we have recently introduced an alternative unit based on a butane-2,3-diacetal (BDA) protection[5] that affords a crystalline aldehyde **2**.[6]



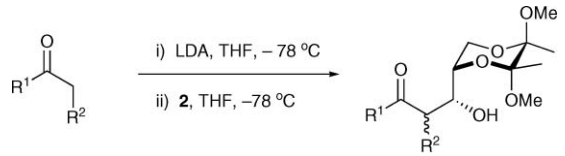
1 **2**

Fig. 1 Glyceraldehyde acetonide **1** and BDA-protected aldehyde **2**.

This protected aldehyde is relatively stable and can be stored at 5 °C for over a year without any noticeable decomposition. It is also easily prepared in either enantiomeric form from cheap starting materials on a large scale.[6c] In earlier work we have investigated the stereoselective addition of Grignard reagents to the BDA aldehyde **2**.[6a] This paper extends that work and here we disclose our results using the BDA-protected aldehyde **2** and two further α-substituted derivatives **5a** and **5b** as well as the methyl ketone **7** as electrophiles in diastereoselective aldol reactions. The protected polyol products resulting from these reactions constitute useful fragments for potential application in various natural product synthesis programmes.

We began these studies by reacting BDA aldehyde **2** with a series of esters and ketones using reaction conditions previously developed for the alkylation of BDA derivatives (Table 1).[6b] The esters and ketones **3a**–**g** were dissolved in THF and deprotonated at −78 °C using lithium diisopropylamide (LDA) in the usual way. A solution of BDA aldehyde **2** in THF was then added and the reaction mixture maintained at −78 °C. A simple aqueous workup gave the crude products **4a**–**g** whose diastereomeric ratios were determined by ^{1}H NMR spectroscopy. In all cases the major product was formed by addition of the enolate from the *Re*-face of the carbonyl group in compound **2** and could be isolated in pure form by silica gel chromatography.

Table 1 Substrate survey



3a–g **4a–g**

Substrate	R^1	R^2	Time/h:m	Yield (%)	Product	d.r.
3a	OMe	H	0:45	62	**4a**	6.5 : 1
3b	O^{t}Bu	H	1:00	83	**4b**	7 : 1
3c	OEt	Et	1:00	59	**4c**	5 : 1 (*anti*)
3d	SPh	H	4:00	35	**4d**	2 : 1
3e	Ph	H	0:45	52	**4e**	6 : 1
3f	^{i}Pr	H	18:00	69	**4f**	10 : 1
3g	Ph	Me	1:00	83	**4g**	3 : 1 (*syn*)

Methyl ester **3a** was obtained in 6.5 : 1 selectivity and 62% yield, while the more bulky *tert*-butyl ester **3b** afforded slightly higher selectivity and in better yield. Thioester **3d** was also investigated in these coupling reactions but resulted in a low yield of product (35%) presumably due to loss *via* an alternative pathway that could involve ketene formation.[7] Selectivity for the addition to the methyl ketones **3e**† and **3f** was 6 : 1 and 10 : 1 in 52 and 69% yields, respectively. In the case of ethyl butyrate **3c** and propiophenone **3g** only two out of the four possible diastereoisomers were formed with modest selectivities of 5 : 1 and 3 : 1, with complete selectivity at the R^2 position according to the Zimmerman–Traxler model (Table 1).[8]

The influence of the counter ion and structure of the base on reaction selectivity was then explored using the enolate of acetophenone **3e** as a nucleophile (Table 2). With lithium as the counter ion, selectivity improved as the bulk of the amine increased such that when lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was used a selectivity of >14 : 1 was observed. This probably arises as a result of complex changes within the mixed aggregates of the enolate and amine.[9] However, increasing the size of the counter ion

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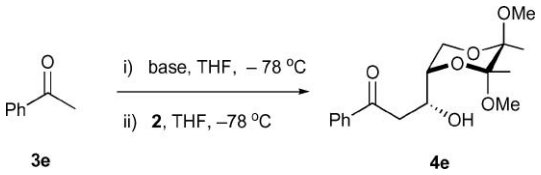
Table 2 Base screening using the enolate of acetophenone **3e** as the nucleophile



3e **4e**

Base	d.r.
LDA	6 : 1
LiHMDS	12 : 1
LiTMP	>14 : 1
NaHMDS	6 : 1
KHMDS	2 : 1

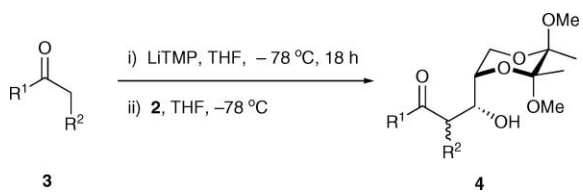
led to a significant decrease in selectivity (2 : 1) when potassium hexamethyldisilazide (KHMDS) was used as the deprotonating base.

The enhanced selectivity for acetophenone using LiTMP led to the investigation of a further series of reactions. Here, enolates generated from esters and ketones were generated using LiTMP as the base, which were then coupled with the BDA aldehyde **2**. Methyl ester **3a** gave 80% yield and a 4 : 1 selectivity whereas the *tert*-butyl ester **3b** derivative afforded product **4b** (53%). Ester **3h** on the other hand gave a 3 : 1 selectivity with total control of the formed stereocentre at R^2 (Table 3). Acetophenone **3e** afforded **4e** in 81% and >14 : 1 selectivity. Propiophenone **3g** led to a 3 : 1 selectivity. Hence LiTMP is superior for the aromatic ketone **3e**, for esters **3a** and **3b** LDA is clearly better.

Next, the scope of the aldol addition was explored using α-substituted BDA aldehydes **5a** and **5b** following the reaction conditions developed above for BDA aldehyde **2** (Table 4). The selectivity of the addition to the methyl substituted BDA aldehyde **5a** was found to be largely independent of the base used. However, a slight overall increase in selectivity was observed for the allyl aldehyde **5b**. In all cases the major product was generated by attack of the enolate from the *Si*-face of the carbonyl group.

The BDA methyl ketone **7** was also investigated as an electrophile using LDA as the base. Here, the reaction of BDA ketone **7** with acetophenone **3e** provided **8e** in 73% yield with >20 : 1 diastereomeric ratio (Table 5). 3-Methyl-butane-2-one **3f** afforded

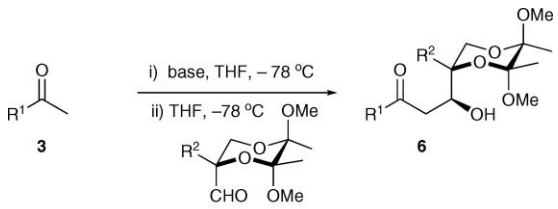
Table 3 Substrate survey using LiTMP as the base



3 **4**

Substrate	R^1	R^2	Yield (%)	Product	d.r.
3a	OMe	H	80	**4a**	4 : 1
3b	O^{t}Bu	H	53	**4b**	4 : 1
3h	O^{t}Bu	Me	69	**4h**	3 : 1 (*anti*)
3e	Ph	H	81	**4e**	>14 : 1
3g	Ph	Me	57	**4g**	3 : 1 (*syn*)

Table 4 Aldol reaction of substituted BDA glyceraldehyde derivatives

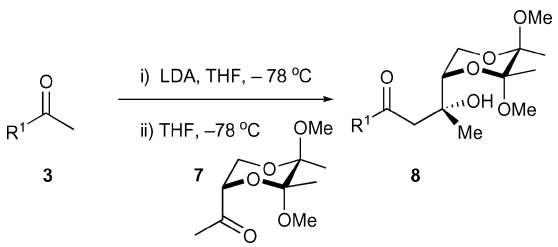


3 **6**

5a R^2 = Me, **5b** R^2 = allyl

Substrate	R^1	R^2	Base	Yield (%)	Product	d.r.
3b	O^{t}Bu	Me	LDA	99	**6b**	2 : 1
3b	O^{t}Bu	Me	LiTMP	50	**6b**	1 : 1
3e	Ph	Me	LDA	95	**6e**	2 : 1
3e	Ph	Me	LiTMP	50	**6e**	2 : 1
3a	OMe	allyl	LDA	60	**6a**	3 : 1
3e	Ph	allyl	LDA	52	**6c**	3 : 1
3e	Ph	allyl	LiHMDS	55	**6c**	2 : 1
3e	Ph	allyl	LiTMP	50	**6c**	2 : 1

Table 5 Scope of the aldol reaction with BDA ketone **7**



3 **7** **8**

Substrate	R^1	Yield (%)	Product	D.r.
3b	O^{t}Bu	15	**8b**	1 : 1
3e	Ph	73	**8e**	>20 : 1
3f	^{i}Pr	88	**8f**	>20 : 1

the major isomer with the same selectivity and in a good 88% yield. The major isomer in this case is formed by attack from the *Re*-face of BDA methyl ketone **7**. The BDA appendage can confer crystallinity on certain products formed and thus aids work-up in these cases. The coupling of *tert*-butyl acetate **3b** with **7** was however poor, the reaction afforded only a 1 : 1 mixture of diastereoisomers **8b** in 15% yield. The reason for this result is not clear.

The stereochemical outcome of these reactions may be explained using the Felkin–Anh model (Fig. 2). In the case of BDA aldehyde **2** the enolate attacks from the *Re*-face with selectivities ranging from 2 : 1 to >14 : 1, whereas there is a slight preference for the substituted methyl and allyl BDA aldehydes **5a** and **5b** to be attacked from the *Si*-face (Table 4). The trend suggests the selectivity increases with the size of the substituent in α-position according to Felkin–Anh control. The stereochemistries were proven by single crystal X-ray diffraction of the *p*-nitrobenzyl esters of **4a**, **4e** and **6a**.

In this work a series of diastereoselective aldol reactions with BDA-protected glyceraldehyde derivates have been disclosed. The reactions generally proceed in good yield and have reasonable selectivity. The products of the reactions are useful as suitably protected building blocks for natural product synthesis, and the

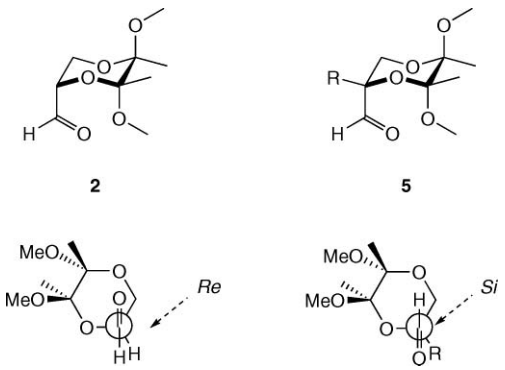


Fig. 2 Stereochemical outcomes explained using the Felkin–Anh model.

procedures clearly complement studies using less stable glyceraldehyde acetonide **1** as a coupling partner.

Acknowledgements

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Notes and references

† Typical experimental procedure for preparation of **4e**: *n*-butyllithium (1.6 M) in hexanes (0.46 mL, 0.75 mmol) was added to diisopropylamine (110 μL, 0.75 mmol) in THF at 0 °C. The reaction was stirred for 15 min then cooled to −78 °C. Then, acetophenone **3e** (88 μL, 0.74 mmol) was added and stirred for 30 min. A solution of BDA aldehyde **2** (250 mg, 0.25 mmol) in THF was cooled to −78 °C then added drop-wise to the enolate. After 45 min the reaction was quenched by adding saturated ammonium chloride and allowing the mixture to warm to rt. The combined organic phase was dried with $MgSO_4$ and evaporated *in vacuo.* The crude mixture was purified by column chromatography using ether–petrol 1 : 3. **4e** (40.5 mg) was obtained in 52% yield in a 6 : 1 diastereomeric ratio. ^{1}H NMR (600 MHz, $CDCl_3$), (major diastereomer), 7.98 (2H, d, $J = 7.3$ Hz), 7.59 (1H, dd, $J = 7.3$, 7.6 Hz), 7.48 (2H, t, $J = 7.6$ Hz), 4.32 (1H, m), 4.01 (1H, dd, $J = 11.0$, 11.0 Hz), 3.95 (1H, dd, $J = 11.0$, 11.0 Hz), 3.90 (1H, m), 3.57 (1H, bs), 3.42 (1H, dd, $J = 17.5$, 17.6), 3.33 (3H, s), 3.30 (3H, s), 3.14 (1H, dd, $J = 17.5$, 17.6), 1.36 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 200.38, 136.83, 133.51, 128.66, 128.15, 99.94, 99.35, 72.20, 69.24, 61.08, 48.83, 48.29, 41.96, 18.20, 17.76; MS 347.16 calculated for $C_{17}H_{24}O_6Na$ found 347.15, $[a]_D = -0.50$ (C = 1, $CHCl_3$).

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