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Stereoselective Addition of Methyl Acrylate to α-Amino Aldehydes

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STEREOSELECTIVE ADDITION OF METHYL ACRYLATE TO α-AMINO ALDEHYDES

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ABSTRACT: Variously N-protected α-aminoaldehydes exhibit reasonable diastereoselectivity in the *Baylis-Hillman coupling*[1] with methyl acrylate to provide either primarily syn or anti α-methylene-β-hydroxy-γ-amino esters.

Stereocontrontrolled aldol strategies have been widely applied to chiral α-amino aldehydes because of the potentially useful multifunctionalised products that result.[2] In contrast to the substantial levels of diastaereoselectivity obtained with chiral α-alkoxycarbonyl systems, the corresponding amino aldehydes have generally exhibited poor stereocontrol in the addition reactions of organometallic reagents. Recently we reported the 3° amine catalysed Baylis-Hillman approach to the anti-diastereoselective[4] coupling of vinyl carbonyl units with various α-alkoxy aldehydes[5] [FIG., Compound 1]. The success of this simple methodology prompted us to examine the analogous protected amino aldehyes under these metal coordination free reaction conditions [FIG., Compounds 2-6].

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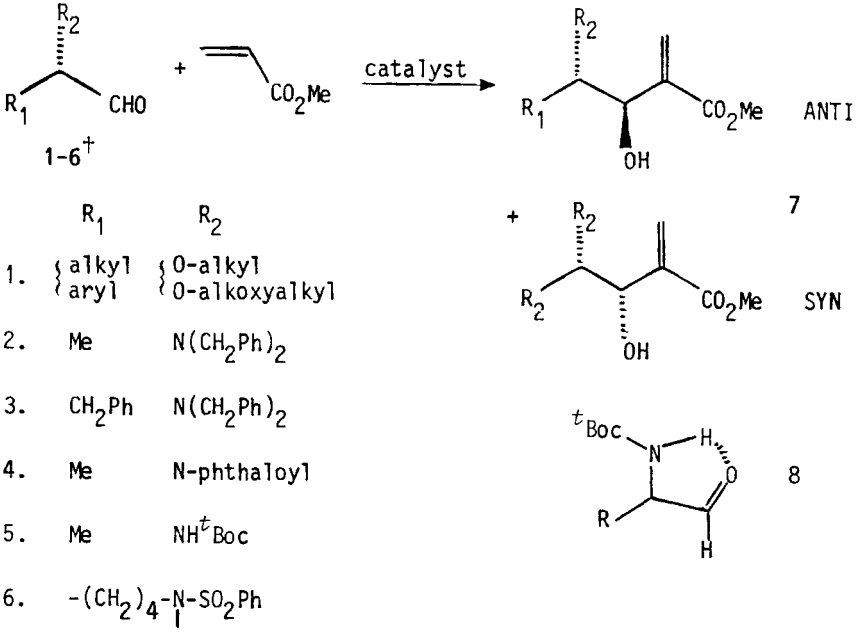
FIGURE



	R_1	R_2
1.	alkyl aryl	O-alkyl O-alkoxyalkyl
2.	Me	$N(CH_2Ph)_2$
3.	CH_2Ph	$N(CH_2Ph)_2$
4.	Me	N-phthaloyl
5.	Me	NH^tBoc
6.	$-(CH_2)_4-$	$N-SO_2Ph$

† For the sake of clarity, only one enantiomer is depicted.

We would here like to report our preliminary study which has been primarily directed at establishing the influence of the choice of the N-protection on the overall reactivity of the aldehyde and on the diastereoselectivity of the coupling. Representative results are shown in the TABLE.

The pattern of aldehyde reactivity was as anticipated, with those having electron withdrawing N-protection showing greater reactivity (viz: Entries 1-3 versus 4-7). The use of molar equivalents of catalyst to obtain synthetically more useful reaction times was prompted by our own observations and a recent publication by the Basavaiah group[6,7].

TABLE

Reactions of N-protected α-amino aldehydes **2-6** with methyl acrylate

ENTRY	ALDEHYDE[a] (M.Mole)	CATALYST[b] (Mole%)[c]	REACTION TIME (Days)	ANTI:SYN RATIO	YIELD[d]
1	2 (1.6)	B (10)	-	-	-[e]
2	2 (22)	A (100)	20	72:28	71
3	3 (19)	A (100)	31	70:30	80
4	4 (39)	A (100)	3.5	55:45	30
5	5 (34)	A (10)	7	26:74	80
6	5 (26)	A (100)	<1.5	29:71	76
7	6 (15.6)	A (100)	<0.5	88:12	55

a Aldehydes used in entries 4 and 5 were racemic

b A = 1,4-diazabicyclo[2.2.2]octane

B = 1-azabicyclo[2.2.2]octan-3-ol

c Based on aldehyde

d Refers to isolated yield after chromatography

e No product was detected after 9 days

The observed diastereoselectivity is dependent on the type of amino group protection. Thus, the anti diastereoselectivity (aldehydes 2, 3, 4, 6) may be rationalised in terms of the Felkin-Anh open chain model[8] and follows that obtained with the α-alkoxy aldehydes. The reversal of selectivity with the NH-Boc aldehyde 5 is probably due to the involvement of the H-bonded structure 8 and is in accordance with earlier reports[2,9] where a proton-bridged Cram cyclic model[10] is thought to account for the syn stereochemical outcome. This protecting group dependant diastereoselectivity further enhances the synthetic utility of this facile coupling reaction.

We are currently exploiting these highly functionalised products within our programme of natural product synthesis.

EXPERIMENTAL

Aldehydes:

N,N-dibenzyl-L-alinal (2)[11], N,N-dibenzylphenyl-L-alinal (3)[11], N-phthaloyl-L-alinal (4)[12], and N-Boc-L-alinal (5)[9] were prepared according to the literature procedures. N-phenylsulphonyl-L-prolinol was prepared from L-proline via benzenesulphonyl chloride protection[13] followed by a standard lithium aluminium hydride reduction - Swern oxidation sequence.

α-Methylene-β-hydroxy-γ-amino esters (7)

General procedure:

The aldehyde (1 equiv.) was added to a mixture of methyl acrylate (4 equiv.) and catalyst (see Table) at ambient temperature. The reactions were stoppered and stirred until ^{1}H nmr indicated consumption of aldehyde. Work-up consisted of, in the case of N,N-dibenzylated products, direct flash chromatography[14] (ethyl acetate/pet. ether 10-30%) or, for all other products, dilution with CH_2Cl_2, sequential wash with 2N HCl and H_2O, and then chromatography of the dried ($MgSO_4$) and reduced organic layer. All new product mixtures gave satisfactory analytical and spectroscopic data.

Ratio analysis by ^{1}H nmr was carried out on the diastereomeric mixtures before and after isolation from the crude reaction mixtures. In some cases the methylene signals between δ 5.5 - 6.5 were amenable to direct analysis but largely the methodology of *in situ* -OH derivatisation with trichloroacetyl isocyanate was

applied.[15] This allowed direct determination of diastereomer ratios and confirmation of the anti and syn nature of the component isomers.

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