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Aldol Addition of Aldehydes - A Stereoselective Approach to *syn*-3-Hydroxyaldehydes

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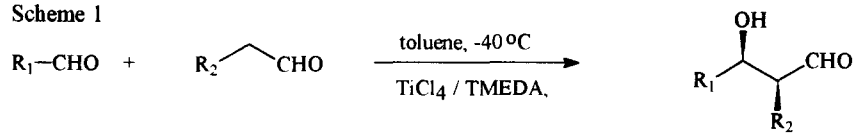
Abstract: *$TiCl_4$-aldehyde complexes undergo aldol addition with enolizable aldehydes in the presence of base. The expected 3-hydroxyaldehydes were obtained with a high degree of syn-selectivity.*

Very little is known concerning aldol addition of enolizable aldehydes to aldehydes.[1] Furthermore, no method is as yet known for diastereoselective aldol addition of aldehyde-enolates to aldehydes.[2] We have found that Lewis-acid complexes of aldehydes will undergo aldol addition in the presence of base. The highest diastereoselectivities, as well as the purest products, were obtained through the utilisation of $TiCl_4$-carbonyl complexes. Although $TiCl_4$ has been previously utilised in other aldol and aldol-type reactions[3], the active hydrogen-component in these published procedures has always consisted of either ketones[4] or carboxylic acid derivatives.[5] Herein we describe for the first time the diastereoselective self-addition of aldehydes and mixed-aldol reactions between two different aldehydes in the presence of $TiCl_4$ and base (Scheme 1).

Scheme 1



R_1	R_2	method / temp (°C)	yield (%)[a]	compound
Ph	Me	B / -10	72	**1**
Ph	Et	B / -10	78	**2**
iso-Pr	Me	C / -20	49[b]	**3**
Et	Me	A / -50	84	**4**

[a] isolated, [b] related to carbonyl compound; method A: the aldehydes were reacted with 4 equiv. of TMEDA and $TiCl_4$; method B: the aldehydes were reacted with 4 equiv. of Et_3N and $TiCl_4$; method C: 4 equiv. of the CH component were complexed with 4 equiv. of Et_3N and $TiCl_4$ at -78°C;1 equiv. of the carbonyl compound was added; the mixture was stirred 1h at -20°C.

Lewis-acid complexes of aldehydes do not undergo aldol addition without the presence of a base. This result is in sharp contrast to what is observed upon the reaction of an aldehyde and a ketone in the presence of Lewis-acids, as bases are not necessary for these complete stereoselective conversions to their corresponding *syn*-aldols.[6, 7]

Aldehydes form $TiCl_4$-complexes which are stable at room temperature and do not form the expected 3-hydroxyaldehydes. However, an aldol reaction is observed at -78°C in the presence of base. At room

temperature, they afforded the corresponding α,ß-unsaturated aldehydes[8] or acetals of the formed aldols.[9] All reaction were carried out in inert solvents such as toluene, dichloromethane or carbon tetrachloride. Greater amounts of side products and diminishing yields were observed in ether-containing solvents, such as tetrahydrofuran or diethylether. Equimolar amounts of bases and Lewis-acids are necessary for a complete conversion to the 3-hydroxyaldehydes. These results are also in contrast to the catalytic aldol addition of aldehydes and ketones in the presence of $TiCl_4$.[6,7]

The reaction of the complexed aldehydes exhibit chemoselectivity. No problems are associated with the utilisation of primary aldehydes in this reaction, but Lieben's rule must be considered when reacting primary with secondary aldehydes.[10] For example, aldol **3** is obtained by the reaction of an excess of complexed active-hydrogen primary aldehyde (propionaldehyde) with one equivalent of the carbonyl compound (isobutyraldehyde).

High *syn*-selectivity of the 3-hydroxyaldehydes was observed in all examples (> 96:4). The relative *syn*-configuration of all products was determined by analysis of ^{1}H-NMR coupling constants and the data of the ^{13}C-NMR spectra.[11]

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11. ^{1}H-NMR δ (300 MHz, $CDCl_3$); **1**: 9.79 (d, J=1.1 Hz, R-CHO), 5.25 (d, J=3.8 Hz, Ph-CHOH-); **2**: 9.69 (d, J=2.0 Hz, R-CHO), 5.05 (d, J=5.1 Hz, Ph-CHOH-); **3**: 9.73 (d, J=0.8 Hz, R-CHO), 3.75 (dd, J=3.1, 8.5 Hz, isoPr-CHOH-); **4**: 9.74 (d, J=0.8 Hz, R-CHO), 4.01 (ddd, J=3.3, 5.3, 7.9 Hz, Et-CHOH-). ^{13}C-NMR δ (75 MHz, $CDCl_3$); **1**: 204.44, 141.49, 128.33, 125.80, 125.13, 72.45, 53.04, 7.44; **2**: 204.99, 140.90, 127.58, 126.63, 126.11, 73.04, 60.08, 17.55, 11.34; **3**: 206.78, 76.56, 50,49, 29.66, 19.87, 18.58, 8.34; **4**: 205.66, 71.65, 50.84, 27.11, 10.27, 6.89.

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