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Titanium(IV) Alkoxide Ligand Exchange with α-Hydroxy Acids: The Enantioselective Aldol Addition

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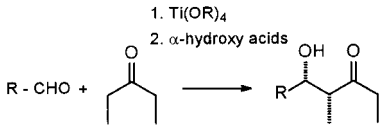
ABSTRACT



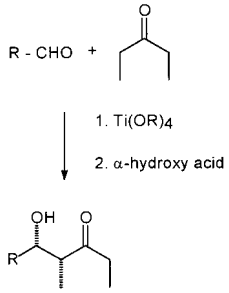
Ligand exchange of titanium(IV) alkoxides with α-hydroxy acids presents an unexpected and novel approach to enantioselective aldol additions of aldehydes and ketones. The aldol products were isolated in a high degree of *syn*-diastereoselectivity. High enantioselectivities were observed by using simple optically pure α-hydroxy acids in this novel aldol addition.

The aldol addition is one of the most powerful synthetic tools available for carbon−carbon bond formation.[1] Although the first known example of an aldol addition, namely, the dimerization of acetone, was an acid-mediated process,[2] most published methods describe aldol additions under basic reaction conditions.[3] The low chemo-, regio-, and stereoselectivity observed using acidic reagents is likely responsible for the few publications within this field.[4] Herein we report a novel and extremely easy enantioselective approach to aldol products in acidic conditions.

In conjunction with our ongoing studies of aldol additions in the presence of titanate complexes,[5] we have observed an unexpected and chemoselective aldol addition of aldehydes and ketones in the presence of titanium(IV) alkoxides and α-hydroxy acids. No products derived from acetalization[6] or by aldol condensation[7] were observed. Furthermore, no *β*-hydroxyaldehydes derived from aldol self-addition of the starting aldehydes were observed[8] and no aldol additions of aldehydes and ketones were observed with only $Ti(OR)_4$ or an α-hydroxy acid alone.

This novel aldol addition was carried out at room temperature in the presence of equimolar amounts of titanium(IV) alkoxides and α-hydroxy acids (Scheme 1). Yields were diminished by the use of titanium(IV) isopropoxide. Partial reduction of the starting aldehyde was observed.

Scheme 1. Aldol Addition Mediated by Titanium(IV) Alkoxides in the Presence of α-Hydroxy Acids



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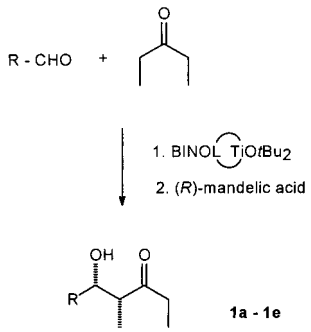
Maximum yield and stereoselectivity were afforded by the use of titanium(IV) *tert*-butoxide. The aldol products **1a**−**1e** were isolated with a high degree of *syn*-diastereoselectivity. Several enantiomerically pure α-hydroxy acids were tested in this procedure, but only low enantioselectivites of the aldol adducts were observed. The use of BINOL−Ti(O*t*Bu)$_2$ in place of Ti(O*t*Bu)$_4$ in these reactions led to enantiomerically enriched aldol products. The best conditions for obtaining high enantioselectivities proved to be the *rac*-BINOL−Ti(O*t*Bu)$_2$/(*R*)-mandelic acid system (Scheme 2).[9]

Scheme 2. Enantioselective Aldol Addition Mediated by the BINOL−Ti(O*t*Bu)$_2$/(*R*)-Mandelic Acid System



This system seems to be selective for the formation of the 4*R* configuration. All isolated aldol adducts were found in the *syn*-4*R*-configuration (Table 1). The use of other enantiomerically pure α-hydroxy acids instead of mandelic acid provided the aldol adducts (*syn*-4*R*-configuration) only with low enantioselectivities (tartaric acid, yield 85%, ee 24%; malic acid, yield 41%, ee 18%; lactic acid, yield 31%, ee 8%).

Table 1. Asymmetric Aldol Addition of Aldehydes with 3-Pentanone[a]

entry	R	product	*syn*/*anti* ratio[b]	ee [%] (config)[c]	yield [%]
1	Ph	**1a**	95/5	93 (4*R*,5*R*)[10]	71
2	*t*Bu	**1b**	85/15	87 (n.d.)	55
3	Ph-≡	**1c**	73/27	94 (n.d.)	72
4	*i*Pr	**1d**	89/11	83 (4*R*,5*S*)[11]	48
5	Et	**1e**	72/28	72 (4*R*,5*S*)[11,12]	76

[a] Reaction conditions: BINOL−Ti(O*t*Bu)$_2$ (1 mmol), aldehyde (1.5 mmol), (*R*)-mandelic acid (1 mmol), 3-pentanone (1 mmol), toluene (0.5 mL), rt.[9] [b] *syn*/*anti* ratio was determined by ^{1}H and ^{13}C NMR spectroscopy. [c] The enantiomeric excess and the configuration of the aldol products were determined by the corresponding MTPA ester. The signals in the ^{1}H and ^{13}C NMR spectra were compared with those obtained by reference substances. The values correspond to those of the major diastereoisomer.

The observed enantioselectivities depended only on the chirality of the starting α-hydroxy acids. No significant influence on the enantioselectivities of aldol adducts (*syn*-4*R*-configuration) were observed by the use of enantiopure BINOL in these reactions with (*R*)-mandelic acid [(*S*)-BINOL, ee 91%; (*R*)-BINOL, ee 89%]. Using (*S*)-mandelic acid, the opposite enantiomer (*syn*-4*S*) of the aldol adducts was observed in only low enantioselectivities (ee < 20%). Bulky ligands other than BINOL used in this reaction (e.g., tetraphenylethanediol, di-*tert*-butyl-*p*-cresol, or triphenylmethanol) also resulted in aldol adducts with low enantioselectivities.

The reaction mechanism is not clear at this time. The titanium(IV) complex in Scheme 2 is intended to indicate a probable transition structure for the observed high *syn*-diastereo- and 4*R*-enantioselectivity. NMR analysis during the reaction indicates a ligand exchange (*t*BuOH versus α-hydroxy acids). This dynamic exchange appears to be prerequisite for the successful execution of the reaction, as preformed complexes of Ti(O*t*Bu)$_4$ and α-hydroxy acids failed to give comparable results. Furthermore, NMR experiments show that the exchange occurs only with the hydroxy group of mandelic acid. No reaction with the carboxylic group itself was observed. Therefore, it is understandable that previous reactions using carboxylic acids without hydroxy groups failed to give aldol addition. This suggested that the hydroxy group is necessary for binding at titanium, freeing the carboxylic group for participation in the enantioselective aldol addition.

Further investigations are underway to elucidate the mechanism of this novel reaction and to utilize this sequence in the synthesis of natural products.

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Supporting Information Available: General procedures and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **Typical experimental procedure:** *rac*-BINOL-Ti(O*t*Bu)$_2$ (480 mg, 1 mmol) was suspended in 0.5 mL of toluene under inert conditions. Freshly distilled isobutyraldehyde (135 μL, 1.5 mmol) was added, and the suspension was stirred at rt until a clear solution appeared (30−60 min). (*R*)-Mandelic acid (160 mg, 1 mmol) was added. The deep brown solution was stirred for 15 min at room temperature. 3-Pentanone (100 μL, 1 mmol) was added. The resulting clear dark brown solution was stirred for a further 5 to 8 h at room temperature. The reaction was monitored by thin-layer chromatography (dichloromethane/acetone 99/1). At the end of the reaction, the mixture was diluted with diethyl ether and quenched successively with aqueous saturated $NaHCO_3$ and NH_4Cl. The organic layer was separated, dried (Na_2SO_4), filtered, and finally concentrated in vacuo. Purification by column chromatography (hexane/ethyl acetate) afforded (4*R*,5*S*)-5-hydroxy-4,6-dimethyl-3-heptanone (**1d**, 76 mg) in 48% yield.
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