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Enantioselective Equilibration–Access to Chiral Aldol Adducts of Mandelic Acid Esters

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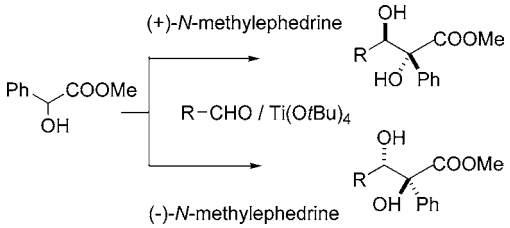
ABSTRACT



Syn-configured aldol products of mandelic acid esters and aldehydes were synthesized by the catalytic use of amines in the presence of titanium(IV) *tert*-butoxide. Used along with chiral *N*-methylephedrine, anti-configured α,β-dihydroxyesters were isolated with a high degree of enantioselectivity for the first time.

The construction of defined chiral quaternary stereocenters has been a continuous challenge in organic chemistry up to now.[1] Cycloadditions, alkylations of ketones, Michael reactions and conjugate additions, allylic alkylation, and cross-coupling reactions have been suitable tools to achieve this goal.[2] Several methods of aldol additions have also been employed successfully for special substrates, but they have failed to be generalized.[3] During our ongoing studies of enantioselective aldol additions in the presence of chiral mandelic acid derivates,[4] chiral 1,2-diols, aldol adducts of aldehydes, and mandelic acid derivatives needed to be synthesized. Little is known about chiral aldol adducts of mandelic acid derivatives,[5] and there are only a few examples in the lactic acid series.[6] We tested several different methods. First, following the classical SRS synthesis of Seebach,[7] we obtained aldol adducts of aldehydes and mandelic acid acetals with moderate enantioselectivities. However, problems of racemization occurred during the deprotection of intermediary acetals.[8] For that reason, we started the syntheses directly with chiral mandelic acid esters.

Porta and Clerici have described an oxidation−reduction approach to aldol adducts of mandelic acid esters starting

(1) For comprehensive reviews, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(2) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005

(3) Schetter, B.; Mahrwald, R. In *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005; pp 51−81.

(4) (a) Mahrwald, R. *Org. Lett.* **2000**, *2*, 4011−4012. (b) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459−4461.

(5) Chiral aldol adducts of ketones and mandelic acid esters were described by: Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283−6287.

(6) (a) For an overview, see: Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH: 1997. (b) Seebach, D.; Naef, R.; Calderari, G. *Helv. Chim. Acta* **1981**, *64*, 2704−2708. (c) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313−1324. (d) Battaglia, A.; Barbaro, G.; Giorianni, P.; Guerrini, A.; Bertucci, C.; Geremia, S. *Chem.−Eur. J.* **2000**, *6*, 3551−3557. (e) Battaglia, A.; Balzelli, E.; Barbaro, G.; Giorianni, P.; Guerrini, A.; Monari, M.; Selva, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1825−1832. (f) For unsatisfying results in aldol additions with aldehydes and mercaptolactic acid, see: Strijtveen, B.; Kellog, M. *Tetrahedron* **1987**, *43*, 5039−5054.

(7) For a comprehensive overview, see: (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem.* **1996**, *108*, 2880−2921. (b) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Sauerlaender: Aarau, 1986; pp 125−259.

(8) A partial retroaldol process during the deprotection of the acetals under basic conditions is assumed as the source of racemization.

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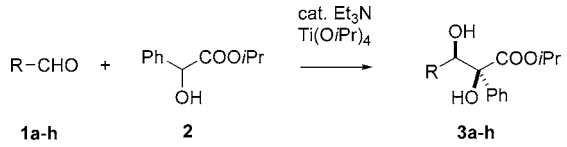
with esters of phenylglyoxylic acid. Using several aldehydes, the expected 1,2-diols were isolated with a high degree of syn- diastereoselectivity.[9] Later on, the same authors published an aldol reaction of mandelic acid esters with aldehydes in the presence of $TiCl_4$ and amines.[10] This method is limited to the use of only *p*-bromobenzaldehyde. We have been able to optimize and extend this procedure by using catalytic amounts of amines in the presence of titanium(IV) alkoxides. An optimized protocol is given in Table 1. Aldol

Table 1. Catalytic and Diastereoselective Aldol Addition[a]



1a-h **2** **3a-h**

entry	R	compd	yield[b] (%)	ratio[c] (syn/anti)
1	Ph	**3a**	88	88:12 (95:5)[d]
2	*t*-Bu	**3b**	86	95:05
3	*iso*-Pr	**3c**	78	94:06
4	Et	**3d**	75	79:21
5	*c*-Hex	**3e**	80	80:20
6	Me	**3f**	70	55:45
7	Ph−CH_2−CH_2−	**3g**	82	57:43
8	Ph−(CH=CH)−	**3h**	60	50:50

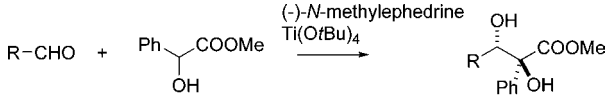
[a] Reaction conditions: 1 equiv of aldehyde, 1 equiv of isopropyl mandelate, 1 equiv of Ti(O*i*Pr)$_4$, rt, 5 mol % of Et_3N. [b] Isolated yields. [c] The diastereoselectivity was determined by ^{1}H NMR analysis and by X-ray structure analysis of **3c**. [d] Diisopropyl ethylamine.

adducts **3a**−**h** of even enolizable aldehydes **1c**−**g** and mandelic acid esters were isolated with high yields and with a high degree of syn diastereoselectivity after 1−2 h at room temperature. The yields of this reaction did not depend on the influence of mandelic esters or titanium(IV) alkoxides used. A slightly increased diastereoselectivity was observed when using diisopropyl ethylamine (entry 1, Table 1). Meerwein−Ponndorf reductions[11] or Tishchenko products[12] were not observed under these conditions. When using chiral mandelic acid esters, no enantioselectivities in the aldol adducts could be detected. Complete racemization was observed in each of our reactions.[13]

Next, we focused our attention on the enantioselective execution of this procedure. Several chiral amines and diamines were used in these reactions without any success in regards to enantioselectivities. In further experiments, we tested several chiral 1,2-aminoalcohols in these reactions.

When used with catalytic amounts of cinchona alkaloids, aldol adducts were isolated in high yields and with a high degree of *syn* diastereoselectivity. The syn-configured aldol products were found in their racemic form. The use of larger amounts of 1,2-aminoalcohols was connected with a change in diastereoselectivity. By using equimolar amounts, we obtained a preference for the anti-configured aldol adducts. The best results so far were obtained by using *N*-methylephedrine. By reacting racemic methyl mandelate **4** with aldehydes **1a**−**k** in the presence of titanium(IV) *tert*-butoxide and optically active methylephedrine, we isolated the anti-configured aldol adducts **5a**−**k** in high yields as well as enantioselectivities (Table 2). By using (+)-*N*-methylephedrine or (−)-*N*-methylephedrine, we were able to obtain both anti-configured enantiomeres, (*R*,*R*)- and (*S*,*S*)-**5a**−**k**. No transesterification[14] was detectable under these reaction conditions.

Table 2. Enantioselective Aldol Addition[a]



1a-m **4** **5a-m**

entry	R	compd	yield[b] (%)	ratio[c] (syn/anti)	ee[d] (anti) (configuration)[e]
1	Ph	**5a**	98	4:96	93 (*S*,*S*)
2	*iso*-Pr	**5c**	88	42:58	72 (*S*,*S*)
3	Et	**5d**	89	51:49	61 (*S*,*S*)
4	*c*-Hex	**5e**	85	61:39	58 (*S*,*S*)
5	*n*-Pr	**5i**	92	40:60	67 (*S*,*S*)
6	*p*-BrC_6H_4−	**5k**	82	10:90	92 (*S*,*S*)

[a] Reaction conditions: 1 equiv of aldehyde, 1 equiv of methyl mandelate, 1 equiv of Ti(O*t*Bu)$_4$, rt, 2 equiv of (−)-*N*-methylephedrine. [b] Isolated yields. [c] The diastereoselectivity was determined by ^{1}H NMR analysis. [d] Enantioselectivities were determined by HPLC on Chiralpak AS and ^{1}H NMR analysis using the Mosher ester technique. [d] The absolute configuration was established by X-ray structure analysis of **5k**.

As pointed out above, the enantio- and diastereoselection that were observed did not depend on the configuration of the mandelic acid esters used. The same enantio- as well as

(9) (a) Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852−2856. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690−1694. (c) Clerici, A.; Clerici, L.; Malpezzi, L.; Porta, O. *Tetrahedron* **1995**, *51*, 13385−13400.

(10) (a) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955−5958. (b) Clerici, A.; Pastori, N.; Porta, O. *J. Org. Chem.* **2005**, *70*, 4174−4176.

(11) For reviews, see: (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007−1017. (b) Graves, D. R.; Campbell, E. J.; Nguyen, S. T. *Tetrahedron: Asymmetry* **2005**, *16*, 3460−3468.

(12) For an overview, see: Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713−1723.

(13) For a study of controlled racemization of mandelic acid derivatives, see: (a) Ebbers, E. J.; Ariaans, G. J. A.; Bruggink, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **1999**, *10*, 3701−3718. (b) The assumption of a chiral induction is based on the following observations. The aldol reaction is completed to the full within 1 h. After the same period, only 20% of the starting chiral isopropyl mandelate has been racemized in comparative experiments of controlled racemization. See Supporting Information. The reason for the total racemization we observed after 1 h is still unclear. Controlled experiments of chiral aldol adduct **3a** in the presence of Ti(O*i*-Pr)$_4$ also indicate a racemization. An exhaustive racemization of **3a** at room temperature was detected after 15 min. Currently, we are not able to discriminate between a racemization of chiral aldol products and a racemic aldol addition.

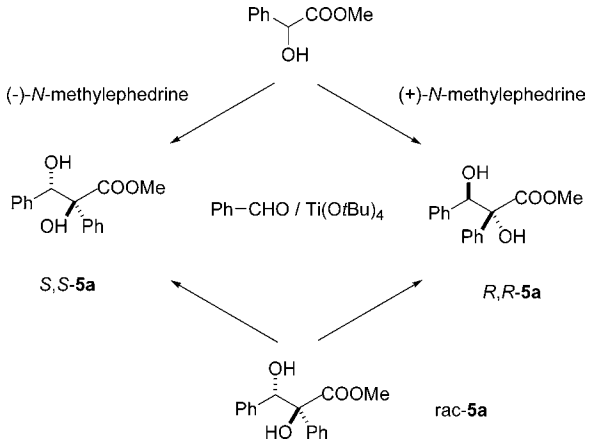
(14) (a) Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138−140. (b) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Sauerlaender: Aarau, 1983; pp 217−353. (c) Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096−7097. (d) dos Santos, A. R.; Ferreira, M. de L. G.; Kaiser, C. R.; Ferezou, J.-P. *Eur. J. Org. Chem.* **2005**, *15*, 3348−3359.

diastereoselectivities were obtained when using (*R*)- or (*S*)-configured mandelic acid esters in these reactions. The enantioselectivities found in these reactions depended only on the chirality of the *N*-methylephedrine used.

To verify that, we reacted racemic anti-configured aldol adduct **5a** with benzaldehyde in the presence of $Ti(O^tBu)_4$ and both (+)- and (−)-*N*-methylephedrine. Both (*R*,*R*)- and (*S*,*S*)-**5a** were isolated with a high degree of enantioselectivity.

Thus, an approach to both enantiomers of anti-configured aldol adducts **5a**−**k** was achieved by the optional use of (+)- or (−)-*N*-methylephedrine (Scheme 1).

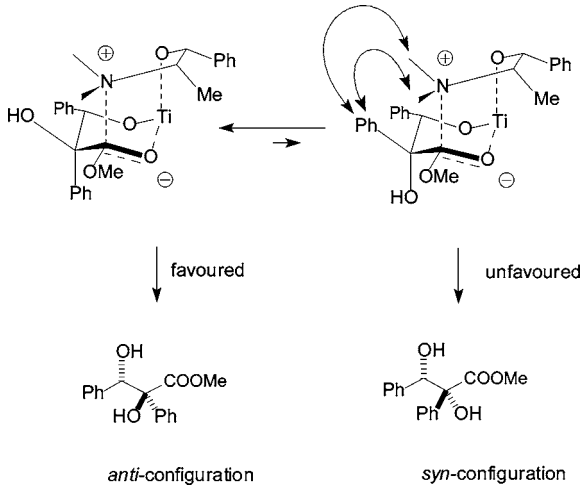
Scheme 1. Optional Approach to (*S*,*S*)- and (*R*,*R*)-Aldol Adducts **5a**



The reactions were completed after 1−2 h at room temperature. After that time, aldol products **5a**−**k** were isolated in high yields with a high degree of syn diastereoselectivity. No enantioselectivities were detected. However, after 24 h at room temperature, anti-configured products **5a**−**k** were isolated in high yields and high enantioselectivities. After that time, only small amounts of syn-configured diols **5a**−**k** were detected as byproducts. The corresponding syn-configured aldol adducts **5a**−**k** were isolated without any enantiomeric excess in all reactions we performed. These unexpected results indicate an enantioselective equilibration during the aldol reaction.[15] On the basis of these findings, a transition-state model is proposed in Scheme 2.

Anti-configured aldol adducts **5a**−**k** were produced under conditions of thermodynamic control. To avoid steric interactions of the dimethylamino group of *N*-methylephedrine,

Scheme 2. Proposed Transition State



the phenyl group of mandelic acid ester occupies the energetically unfavored axial position.[16]

Further experiments of extension and optimization have revealed that this reaction is much more general. Also, esters of lactic acid, malic acid, and tartaric acid are useful substrates for this transformation. Full results of this investigation will be published in a separate, forthcoming paper.

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Supporting Information Available: NMR data of all synthesized compounds and full characterization of novel compounds as well as selected X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) For racemization during aldol equilibration, see also: Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2259−2261. (b) Equilibration in the presence of an iodonium ion: Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667−4672. (c) In the presence of HMPA: Carlier, P. R.; Lo, C. W. S.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443−2445. (d) In the presence of $Ti(O^iPr)_4$: Wang, W.; Digits, C. A.; Hatada, M.; Narula, S.; Rozamus, L. W.; Huestis, C. M.; Wong, J.; Dalgarno, D.; Holt, D. A. *Org. Lett.* **1999**, *1*, 2033−2035.

(16) Support for this proposed model is given by transition-state models of intramolecular ester hydrolysis. See: Brown, R. S.; Aman, A. *J. Org. Chem.* **1997**, *62*, 4816−4820.