JOC Article

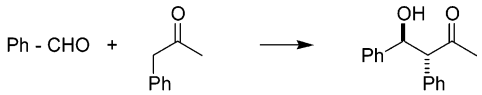
Tetranuclear BINOL−Titanium Complex in Selective Direct Aldol Additions

Bernd Schetter,[†] Burkhard Ziemer,[†] Gregor Schnakenburg,[‡] and Rainer Mahrwald*[,†]

Institut für Chemie der Humboldt-Universität zu Berlin, Brook-Taylor-Strasse 2, 12489 Berlin, Germany, and Institut für Anorganische Chemie der Universität Bonn, Gerhard-Domagk-Straβe 1, D-53121 Bonn, Germany

rainer.mahrwald@rz.hu-berlin.de

Received July 20, 2007



0.2 mol % $Ti_4(\mu\text{-BINOLato})_6(\mu_3\text{-OH})_4$, yield: 78 %;
regioselectivity: > 95:5; d.r. > 95:5

The extremely robust and water-stable tetranuclear complex $Ti_4(\mu\text{-BINOLato})_6(\mu_3\text{-OH})_4$ (**1**) catalyzes the direct aldol addition with high degrees of regioselectivity at the sterically more encumbered α-side of unsymmetrical ketones. The formation of quaternary stereocenters is described. Oxygen-containing ene components can also be used as starting material in these reactions. When used with aliphatic aldehydes, acetals **18** or acetals of aldol adducts **20** were observed. As few as 0.2 mol % loadings with this catalyst **1** were enough to complete the reactions. Mechanistical aspects of the reactions are discussed.

Introduction

An abundance of titanium catalysts for carbon−carbon bond-formation processes have been the area of an intensive research over the past 2 decades.[1] In particular the aldol addition excels as one of the most powerful methods in this field.[2] The direct aldol addition in the presence of metal catalysts represents a biomimetic aldol process. Since the mid-1990s, various methods for direct aldol additions have been developed.[3] However, most of the Lewis acid catalysts that have been employed are sensitive to air and/or moisture, causing extended expenditure in handling. On the other hand, quenching the reactions with water often causes the decomposition of the moisture-sensitive catalysts. The decomposition products, such as BINOL, render the purification of the reaction products more difficult. The recovery of the catalyst also proves impossible in these cases. Other catalysts are produced in situ, preventing reproduceable reaction conditions as well as making mechanistic studies difficult.[4] Last but not least, many catalysts are only accessible by complicated multistep reaction sequences or need rare and expensive metals as reactive reagents.[5] Recent research has focused on the development of stable and storable catalysts, and first remarkable results have been presented by Kobayashi et al.,[6] who presented air- and water-stable rare earth and zirconium catalysts for Mannich, aza Diels−Alder, and Mukaiyama aldol reactions. Bull et al. described the deployment of a moisture-stable titanium triflate in aza-Diels−Alder reactions.[7] Recently, we published preliminary results of the catalytical use of Mikamis tetranuclear titanium cluster **1** in aldol chemistry and presented the first air-stable catalyst for highly regioselective and direct aldol additions in a preliminary note.[8] This catalyst **1** is crystalline and stable

[†] Institut für Chemie der Humboldt-Universität zu Berlin.
[‡] Institut für Anorganische Chemie der Universität Bonn.

(1) For an overview see the following. (a) Acid catalysis: Yamamoto, H.; Futatsugi, K. *Angew. Chem.* **2005**, *117*, 1958. (b) Mikami, K.; Terada, M. In *Lewis Acids in Organic Synthesis*; Hisashi, Y., Ed.: Wiley-VCH: Weinheim, 2000. (c) Titanium complexes: Mikami, K.; Matsumoto, Y.; Shiono, T. In *Science of Synthesis*; Bellus, D., Jacobsen, N. E., Ley, S. V., Noyori, R., Regitz, M., Reider, P. J., Schaumann, E., Shinkai, I., Thomas, E. J., Trost, B. M., Eds.: Thieme: Stuttgart, 2003; Product class 10: Organometallic Complexes of Titanium. (d) Applications to organic synthesis: *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.: Wiley-VCH: Weinheim 2002. (e) *Transition Metals For Organic Chemistry: Building Blocks and Fine Chemicals*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004. (f) Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126. (g) Skato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(2) (a) Heathcock, C. H., Chapter 1.6; Kim, B. M., Williams, S. F., Masamune, S., Chapter 1.7; Rathke, M. W., Weipert, P., Chapter 1.8; Paterson, I., Chapter 1.9; Gennari, C., Chapter 2.4 In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.: Pergamon: Oxford, 1993, Vol. 2. (b) Braun, M. In *Houben-Weyl, Methoden der Organischen Chemie*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. E21b, p 160. (c) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (d) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004. (e) Schetter, B.; Mahrwald, R. In *Quaternary Stereo Centers−Challenges for Organic Synthesis*; Christoffers, J., Baro, A., Eds.: Wiley-VCH: Weinheim, 2005; p 51.

10.1021/jo7014054 CCC: $40.75
Published on Web 01/08/2008

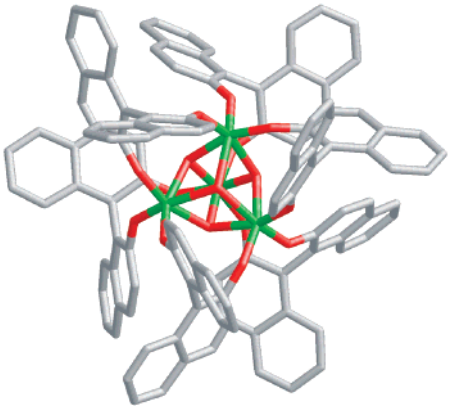


FIGURE 1. Crystal structure of the tetranuclear titanium complex *rac*-$Ti_4(\mu$-BINOLato$)_6(\mu_3$-OH$)_4$ **1**; hydrogen atoms are omitted for clarity.

even against boiling 1 N HCl and 1 N LiOH in dioxane and easy to synthesize from Ti(O*i*Pr)$_4$, *R*-BINOL or *S*-BINOL, and water.[9] We have synthesized this catalyst **1** with *rac*-BINOL[10] and found that all the six BINOL molecules that are incorporated in each cluster have the same configuration. No clusters appeared in crystalline form with mixed configuration of the incorporated BINOLs (Figure 1).

Results and Discussion

Only a very limited number of applications of catalyst **1** in organic reactions are known (cycloadditions,[9a] asymmetric ene reactions,[9b,c] and enantioselective sulfoxidation[9d]).

To test the applicability of this titanium complex **1** in aldol additions, we reacted several aromatic and aliphatic aldehydes with symmetric and unsymmetric ketones **3**. In fact, the complex was able to catalyze the direct aldol addition between aromatic aldehydes **2a**−**f** and unsymmetric ketones **3** in a remarkably clean way. Even very low catalysts loadings[11] (0.2 mol %) yielded aldol adducts **4a**−**m** (Table 1).[12]

This reaction was found to be highly regioselective. Aldol addition is strongly preferred at the sterically more encumbered α-carbon atom of the ketone. In many cases only one regioisomer could be detected. Methyl groups of alkan-2-ones were found to be unaffected under these reaction conditions. The determination of structure of aldol adducts **4a**−**m** and regioisomers **4a**−**m** was achieved by analysis and comparison of ^{1}H and ^{13}C NMR spectra with data reported in the literature.[13]

Initially, the mechanistical aspects of this high regioselectivity were tried to explain by electronical effects, which render the intermediate formation of enolates at the methyl group unfavorable.[14] Subsequent competition experiments of reaction mixtures containing 1 equiv of acetone and 1 equiv of methyl ethyl ketone with 1 equiv of benzaldeyde yielded a ratio of 48:15:3 for **4b**:**4n**:**4o** (**4b**: R^1 = Ph, R^2 = Me, R^3 = R^4 = H; **4n**: R^1 = Ph, R^2 = R^3 = R^4 = H; **4o**: R^1- = Ph, R^2 = R^3 = H, R^4 = Me, Table 1). First, these results demonstrate the high regioselectivity described for aldol adducts **4b**:**4o** (48:3). Also, these results indicate that the methyl group of acetone reacts five times faster than the methyl group of methyl ethyl ketone (**4n**:**4o** = 15:3). Moreover, the ratio observed is time-independent. Same ratio is detected in the very first 3−4 h or after 10 days. No thermodynamic equilibration is observed. These observations make electronic effects a sole explanation for the high regioselectivities obtained untenable.

This unusual regioselective outcome of the reaction with methyl ketones can be explained by steric aspects at best (Figure

(3) (a) Mahrwald, R. *Chem. Ber*. **1995**, *128*, 919. (b) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem., Int. Ed. Engl*. **1997** *36*, 1871. (c) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733. (d) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (e) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Oshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 2466. (f) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 2569. (g) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem*. **2002**, *67*, 2556. (h) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 2169. (i) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (j) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (k) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666. (l) Trost, B. M.; Yeh, Y. S. C. *Org. Lett.* **2002**, *4*, 3513. (m) Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori R. *Tetrahedron Lett.* **2001**, *42*, 4669. (n) Mahrwald, R. *Org. Lett*. **2000**, *2*, 4011.

(4) (a) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (b) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861. (c) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, 267. (d) Delas, C.; Szymoniak, J.; Lefranc, H.; Moïse, C. *Tetrahedron Lett.* **1999**, *40*, 1121. (e) De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187. (f) Davis, J. T.; Balsells, J.; Caroll, P. J.; Walsh, P. J. *Org. Lett*. **2001**, *3*, 699. (g) Zimmer, R.; Peritz, A.; Czerwonka, R.; Schefzig, L.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 3419. (h) Villano, R.; De Rosa, M.; Salerno, C.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1949. (i) Villano, R.; Acocella, M.; De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry*, **2004**, *15*, 2422.

(5) (a) Sawamura, M.; Ito, Y. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc*. **1986**, *108*, 6405. (c) Ito, Y.; Sawamura, M.; Hayashi, T. *Terahedron Lett.* **1987**, *28*, 6215. (d) Sawamura, M.; Ito, Y. *Catal. Asymmetric Synth.* **1993**, 367.

(6) (a) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 12236. (b) Kobayashi, S.; Ueno, M.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5476.

(7) Bull, S. D.; Davidson, M. G.; Johnson, A. L.; Robinson, D. E. J. E. Mahon, M. F. *Chem. Commun.* **2003**, 1750.

(8) Mahrwald, R.; Schetter, B. *Org. Lett.* **2006**, *8*, 281.

(9) (a) Mikami, K.; Ueki, M.; Matsumoto, Y.; Terada, M. *Chirality* **2001**, *13*, 541. (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267. (c) Pandiaraju, S.; Chen, G.; Lough, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2001**, *123*, 3850. (d) Pescitelli, G.; diBari, L.; Salvatori, P. *J. Organomet. Chem.* **2006**, *691*, 2311.

(10) The experimental procedure was the same as that given by Mikami et al. The catalyst was obtained as dark red rectangular crystals. A single crystal structure analysis was made of a suitable crystal. The complex was found to crystallize in the cubic space group *F*43*c*. $a = b = c = 32.348$ Å; $R1 = 0.049$, $wR2 = 0.118$. Crystallographic data have been deposited at the Cambridge Crystal Data Centre (CCDC 279234). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge 1EZ, U.K. (http://www.ccdc.cam.ac.uk; email: deposit@ccdc.cam.ac.uk). The structure was refined with SHELX97 (Sheldrick, G.M. *SHELX97. Program for the Refinement of Crystal Structures*; Universität Göttingen: Göttingen, 1997.)

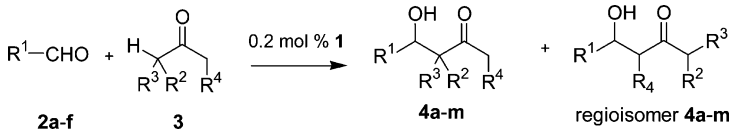
(11) So far, the catalysts loadings for similar reactions range usually between 2 and 20 mol %; recently, Ding et al. presented an enantioselective carbonyl−ene reaction with comparable low catalyst loadings: Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 5478.

(12) **Typical Experimental Procedure.** One equivqlent of aldehyde and 1.5 equiv of ketone were mixed at room temperature. If problems with the solubility occured, small amounts of CH_2Cl_2 were used as solvent, then 0.2 mol % of the catalyst was added. The progress of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether and the reaction was quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. Column chromatography (hexane/ethyl acetate) afforded the pure aldols. Yields have not been optimized. Large amounts of recovered aldehyde indicate the necessity to use longer reacion times or higher reaction temperatures in some cases.

(13) See Supporting Information.

(14) Roy, R. K.; Tajima, N.; Hirao, K. *J. Phys. Chem. A* **2001**, *105*, 2117.

TABLE 1. Direct and Regioselective Aldol Additions of Aromatic Aldehydes to Unsymmetrical Ketones



entry	R^1	R^2	R^3	R^4	product	regioselectivity[a] (**4a**−**m**:regioisomers **4a**−**m**)	yield (%) of **4a**−**m**	*syn/anti* ratio of **4a**−**m**
1	Ph	*n*-Bu	H	H	**4a**	97:3	68	18:82
2	Ph	Me	H	H	**4b**	95:5	74	53:47
3	Ph	Me	H	Me	**4c**		85	50:50
4	Ph	Ph	H	H	**4d**	>95:5[b]	78	<5:95
5	Ph	Me	Me	Me	**4e**	51:49	22[d]	
6	Ph	Me	Cl	H	no reaction			
7	PhC≡C	Me	H	H	**4f**	>95:5[b]	88	67:33
8	PhC≡C	Me	Me	Me	**4g**	60:40	56[e]	
9	4-EtO−C_6H_4	Me	H	H	**4h**	95:5	55	50:50
10	4-EtO−C_6H_4	*n*-Bu	H	H	**4i**	>95:5[b]	71	10:90
11	4-Cl−C_6H_4	Me	H	Me	**4k**		54	57:43
12	3-MeO−C_6H_4	Me	H	Me	**4l**		64	50:50
13	α-thiophenyl	Me	H	H	**4m**	>95:5[b]	24[c]	38:62

[a] Ratio was detected by NMR experiments. [b] Regioselectivity was generally below the detection limit of 300 MHz ^{1}H NMR (>95:5). [c] 70% of the thiophenecarbaldehyde was recovered. [d] 75% of the benzaldehyde was recovered. [e] 40% of the phenylpropargyl aldehyde was recovered.

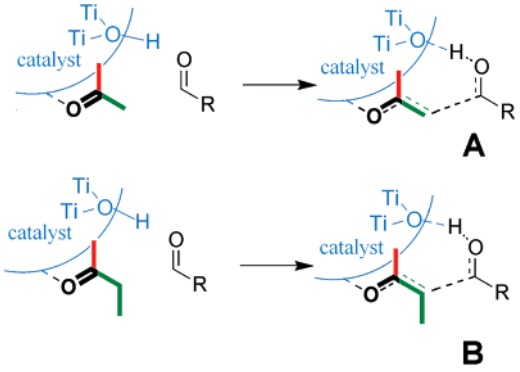


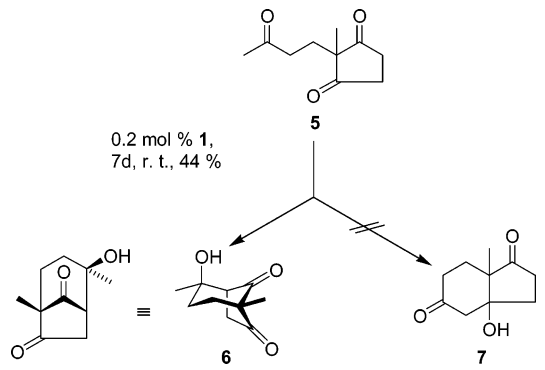
FIGURE 2. Working model for the explanation of the high regioselectivities. Blocked side of the ketone is shown in red; acessible side of the ketone is shown in green.

2). It is assumed that in a first coordination step the less sterically encumbered side of the ketone (red) is turned toward to the catalyst. At this stage the more encumbered side (green) is accessible for the attack by an aldehyde. This assumption allows the minimization of steric interactions between catalyst and methyl ketones. Also, this working model explains the fact that the methyl groups of alkan-2-ones are almost inert (structure B, Figure 2), whereas the methyl group of acetone is more reactive (structure A, Figure 2). Even in the extremely unfavored case with 2-methyl diethylketone the reaction still proceeds at the more encumbered α-position of the ketone, though with lower selectivities (entries 5 and 8, Table 1). In contrast to that, electronic reasons are supposed to be responsible for the striking behavior of 3-chlorobutan-2-one to act as an ene component in these reactions (entry 6, Table 1).

This reaction behavior was also observed in intramolecular aldol additions. The Wieland−Miescher ketone **5** avoids the typically aldol cyclization to the CD-bicyclic steroidal intermediate **7** (Scheme 1).[15] Instead of the expected formation of the bicyclic dione **7**, only dione **6** could be detected with a high degree of diastereoselectivity (>95:5). Dione **6** possesses two

(15) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

SCHEME 1. Formation of Bicyclic Diketone 6 Is Strongly Preferred over Formation of Wieland−Miescher Ketone 7



quaternary stereocenters with defined relative configuration (*endo*-CH_3, *exo*-OH, Figure 3).[16]

Other quaternary carbon atoms were also synthesized by reacting aromatic aldehydes **2a**−**e** with 2-methylcyclopentanone **8** (Table 2) and 2-methylcyclohexanone **11** (Table 3). The regioselectivities in these reactions depend upon the nature of the cyclic ketone. Aldol adducts of 2-methylcyclopentanone **8** are formed with higher degrees of regioselectivity than aldol adducts of the 2-methylcyclohexanone series. The configurations of aldol adducts **9a**−**e** and **10a**−**e** were established by comparing chemical shifts and coupling constants of signals in the ^{1}H NMR spectra with those of *syn*-configured aldol adduct **9d**. The configuration of aldol adduct *syn*-**9d** was established unambigously by a X-ray crystal structure analysis (Figure 4).

The configurations of aldol adducts **12a**−**e** and **13a**−**e** were established by comparing chemical shifts and coupling constants of signals in the ^{1}H NMR spectra with spectral data of **12a** and **13a** reported in the literature.[17]

(16) The relative stereochemistry was unambigously determined by single crystal structure analysis. Substance **6** crystallizes in the orthorhombic space group $Pna2_1$. a = 12.024 Å, b = 10.6931 Å, c = 7.1249 Å; $R1$ = 0.025, $wR2$ = 0.061. Crystallographic data have been deposited at the Cambridge Crystal Data Centre (CCDC 279235). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge 1EZ, U.K. (http://www.ccdc.cam.ac.uk; email: deposit@ccdc.cam.ac.uk).

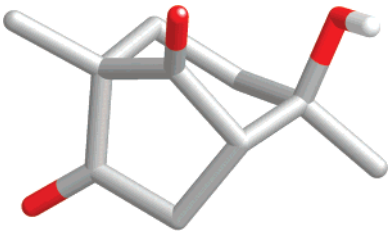


FIGURE 3. Crystal structure of the bicyclic diketone **6**.

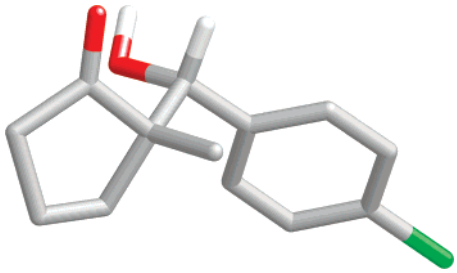
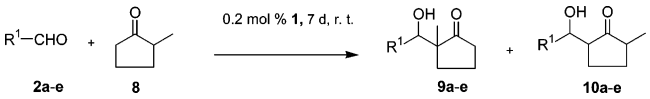


FIGURE 4. Crystal structure of aldol *syn*-**9d**.

TABLE 2. Direct and Regioselective Aldol Additions to 2-Methylcyclopentanone



2a-e 8 9a-e 10a-e

entry	R^1	regio-selectivity **9**:**10**	*syn*-**9**:*anti*-**9**	overall yield (%)
1	**a**: Ph	>95:5[a]	52:48	85
2	**b**: PhC≡C	94:6	51:49	81
3	**c**: 4-EtO−C_6H_4	>95:5[a]	65:35	61[b]
4	**d**: 4-Cl−C_6H_4	96:4	55[c]:45	68
5	**e**: 3-MeO−C_6H_4	96:4	67:33	68

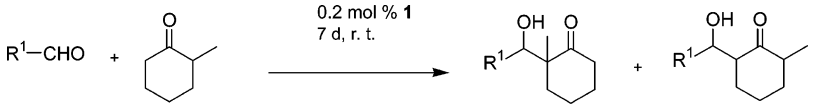
[a] Regioselectivity was generally below the detection limit of 300 MHz ^{1}H NMR (>95:5). [b] 28% of the aldehyde were recovered. [c] Relative configuration was determined by X-ray structure analysis.

Next, we focused our attention on direct aldol additions with oxygen-containing ene components. In contrast to the regioselective $TiCl_4$-mediated direct aldol addition,[18] this reaction is applicable even to hydroxylated ene components, but great differences in the outcome of reactions were observed depending on conditions and substrates. Hydroxyacetone **14** reacts with aromatic aldehydes **2a**−**i** to yield the protected *syn*- and *anti*-configured aldol adducts **16a**−**i**. (Table 4). This reaction also proceeds highly regioselectively; only one regioisomer could be detected. The attack of aldehydes **2a**−**i** was observed exclusively at the oxygen-containing α-position of hydroxyacteone **14**. The outcome of this reaction was found to be time-dependent. Shorter reaction times yield the kinetically favored products **15** (acetals of aldol adduct **17**, Scheme 2). These products can be isolated, but they are not stable at room temperature. Retro-acetalization takes place, and the unprotected aldol adducts **17** as well as free aldehydes **2a**−**i** and hydroxyacetone **14** can be detected. The acetalization process (step 2) proceeds quickly and smoothly. Even isolated and unprotected aldol adducts **17** react with aldehydes under the same reaction conditions to give acetals **15**. This observations make it likely that the aldol process (step 1) is the rate-determining step of the reaction sequence, followed by the much faster acetalization (step 2).

Longer reaction times and higher temperatures favored the formation of thermodynamically preferred ketals **16a**−**i**. Formally, these products were produced by an aldol/ketalization process with hydroxyacteone **14**. The ketals **16a**−**i** are stable; no retroketalization is observed. In summary, under kinetic reaction control acetalization of aldol adduct **17** is obtained, whereas under thermodynamic reaction control ketals **16a**−**i** of aldol adduct **17** were observed. Ketalization of isolated aldol adduct **17** with hydroxyacetone **14** did not proceed under the described reaction conditions. Therefore we assume the existence of further intermediates, which yield the ketals **16a**−**i** via reaction step 4. These intermediates could be formed from the educts (step 3) as well as from the intermediately formed free aldol adducts **17** (step 5). Generally it was found that a 5-fold excess of aldehyde **2a**−**i** and prolonged reaction times was the best way to obtain aldol adducts **16a**−**i** and to supress the selfaldol reaction of hydroxyacetone **14** (see below). The configurations of products *syn*-**16a** and *anti*-**16a** were confirmed by a X-ray crystal structure analysis. (Figures 5 and 6). The structure of *syn*-**16b**−**h** and *anti*-**16b**−**h** were established by comparison of chemical shifts and coupling constants with those of *syn*-**16a** and *anti*-**16a**.

In contrast to the aromatic series enolizable aldehydes react in a different way. When non-oxygen-containing ene components **3**, **8**, and **11** were used as starting material, trimerization of the starting aldehydes **2a**−**e** was observed at room temperature. The corresponding trioxanes **18a**−**e** were isolated with high yields (Table 5). The structure of trioxanes **18a**−**e** was determined by comparison of spectral data with those reported in the literature.

TABLE 3. Direct and Regioselective Aldol Additions to 2-Methylcyclohexanone

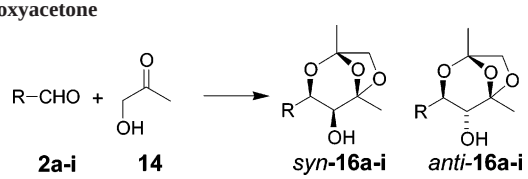


2a-e 11 12a-e 13a-e

entry	R^1	regioselectivity[a] **12**:**13**	*syn*-**12**: *anti*-**12**	*syn*-**13**: *anti*-**13**	overall yield (%)
1	**a**: Ph	66:34	55:45	72:28	53[b]
2	**b**: PhC≡C	78:22	52:48	70:30	72
3	**c**: 4-EtO−C_6H_4	no reaction			
4	**d**: 4-Cl−C_6H_4	81:19	65:35	67:33	34
5	**e**: 3-MeO−C_6H_4	75:25	63:37	65:35	12[c]

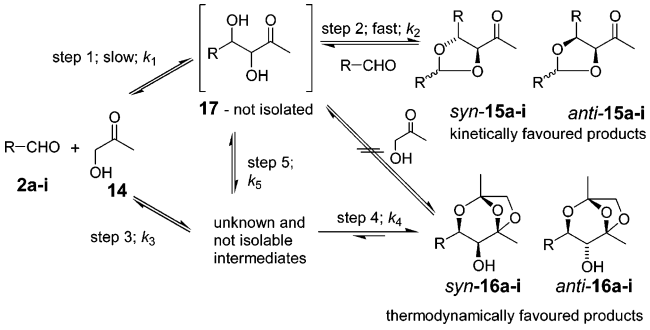
[a] Ratio was detected by NMR experiments. [b] 38% of the aldehyde was recovered. [c] 78% of the aldehyde were recovered.

TABLE 4. Direct and Regioselective Aldol Additions to Hydroxyacetone



entry	R	yield **16** (%)	*syn*-**16**: *anti*-**16**
1	**16a**: Ph	67	16:84
2	**16b**: PhC≡C	63	20:80
4	**16c**: 4-EtO−C_6H_4	41	15:85
5	**16d**: 4-Cl−C_6H_4	70	32:68
6	**16e**: 3-MeO−C_6H_4	66	19:81
7	**16f**: α-thiophenyl	12	24:76
8	**16g**: 2,4-Me_2-C_6H_4	35	17:83
9	**16h**: 4-MeO−C_6H_4	33	27:73
10	**16i**: 4-NO_2−C_6H_4	no reaction	

SCHEME 2. Direct Aldol Additions of Hydroxyacetone with Nonenolizable Aldehydes



In contrast to these results, aliphatic aldehydes **2a**−**h** reacted immediately with oxygen-containing ene components such as hydroxyacetone **14** to the corresponding ketalacetals **19a**−**h** (Table 6). The ketalacetals **19a**−**h** were found to be moisture-sensitive and were obtained in moderate to good yields. The degree of *syn*-diastereoselectivity observed in this reaction depends on the nature of the starting aldehyde **2a**−**h**. When using aldehydes with bulky residues higher *syn*-diastereoselectivities were detected (entries 4,6, and 7, Table 6). In reactions with α-chiral racemic aldehydes **2f** and **2g**, four diastereoisomeres were isolated (entries 6 and 7, Table 6). No 1,2-asymmetric induction could be detected during these experiments. Both *syn*-configured **19f** and **19g** as well as *anti*-**19f** and **19g** were isolated as diastereomeric mixtures of 1:1. The structure of trioxanes **19a**−**e** was determined by comparison of spectral data with those of compound **19d**. The configuration of compound **19d** was determined by NOE experiments. These experiments were carried out especially with acetal **19d**, since intensive NOE effects occurred in this case due to the bulky *tert*-butyl group.[19]

It has to be pointed out that the one-step-synthesis to these acetals represents a great improvement, since currently acetal **20a** has to be synthesized by a more complicated multistep reaction sequence.[20]

When this reaction was carried out over longer periods and at higher temperatures, again products derived from an aldol addition were observed (Table 7). Acetalprotected aldol adducts **20a**−**d** of hydroxyacetone **14** were isolated in good yields.

(17) Ward, D. E.; Sales, M.; Sasmal, P. K. *J. Org. Chem.* **2004**, *69*, 4808.

(18) Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413.

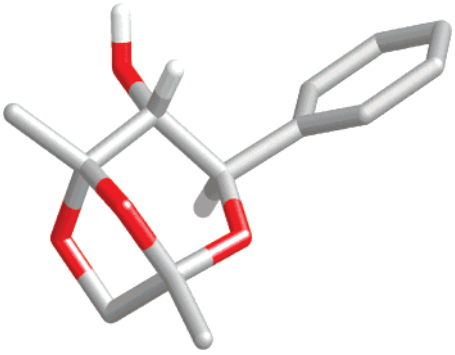


FIGURE 5. Crystal structure of protected aldol adduct *anti*-**16a**.

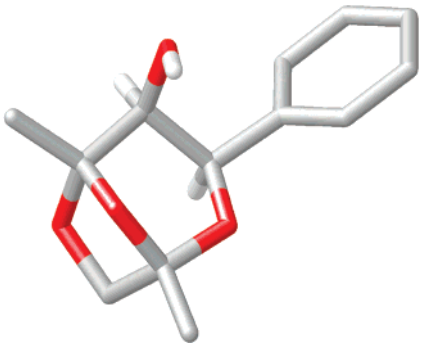
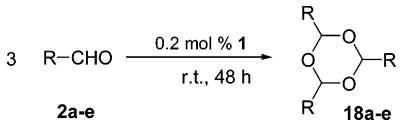


FIGURE 6. Crystal structure of protected aldol adduct *syn*-**16a**.

TABLE 5. Formation of Trioxanes in in the Presence of Complex 1



entry	R	yield (%)
1	**a**: Et	51
2	**b**: *i*Pr	70
3	**c**: Cy	90
4	**d**: Ph-$(CH_2)_2$-	45
5	**e**: r*ac*-Ph−CHMe-	77

In addition, hydroxyacetone **14** reacts in the absence of aldehydes to the hydroxyketone protected self-aldol adduct **22** (Scheme 3). Formally **22** stems from ketalization of intermediate aldol adduct **21**. The unprotected selfaldol adduct could not be detected under these reaction conditions. Notably, only one regio- as well as diastereoisomer of the protected aldol adduct **22** was observed and isolated with 55% yield. The relative configuration of **22** was determined by NOE experiments. The following calculations resulted in the geometry-optimized structure presented in ref 21.

(19) Stereochemical investigation of the ketalacetal **19d** and determination of the relative stereochemistry. NOE effects are visualized with green arrows. See Supporting Informations.

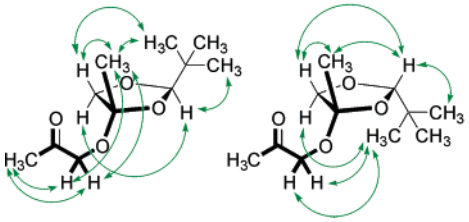
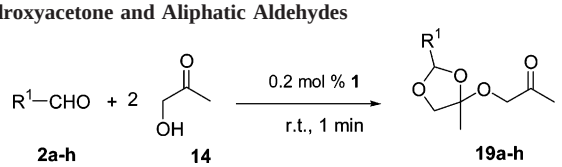


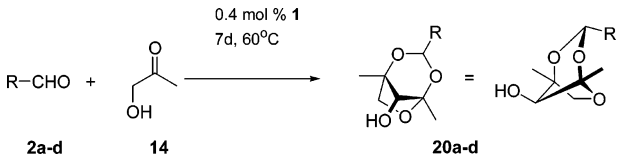
TABLE 6. Kinetically Controlled Formation of Ketalacetals of Hydroxyacetone and Aliphatic Aldehydes



entry	R	yield (%)	*syn*-**19**:*anti*-**19**
1	**a**: Me	32	62:38
2	**b**: Et	62	65:35
3	**c**: *i*Pr	70	67:33
4	**d**: *t*Bu	49	84:16
5	**e**: Cy	53	69:31
6	**f**: *rac*-Et-CHMe-	46	69:31[a]
7	**g**: *rac*-*n*Pr-CHMe-	34	70:30[a]
8	**h**: Ph-$(CH_2)_2$-	20	65:35

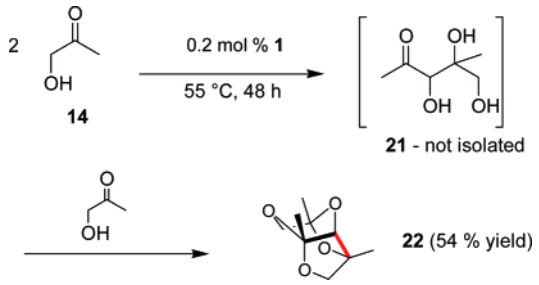
[a] Internal diastereoselectivity 50:50.

TABLE 7. Thermodynamically Controlled Formation of Ketalacetals 20 of Hydroxyacetone and Aliphatic Aldehydes



entry	R	yield (%)
1	**a**: Ph-$(CH_2)_2$-	25
2	**b**: *i*Pr	25
3	**c**: Cy	34
4	**d**: *t*Bu	32

SCHEME 3. Trimerization of Hydroxyacetone; New C−C Bond Is Indicated in Red



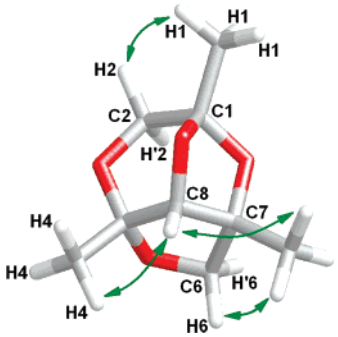
Because tetranuclear titanium catalyst **1** is extremely resistant to air, moisture, and acids, neither drying of the reagents and the solvents nor the application of protection gas techniques were necessary. Although the reaction stopped after adding 1 equiv of water, the aldol reaction proceeded after removing water (3 Å molecular sieves after separation of the aqueous layer), indicating that the catalyst remained stable and active. It was even possible to recover unchanged catalyst from the reaction mixture. Higher reaction temperatures and higher catalysts loadings accelerated the reaction rates in many cases, but it has to be pointed out that this advantage is generally associated with greater amounts of byproducts, lower selectivities, and lower yields. Further experiments concerning the concept of chiral amplification and chiral poisoning[22] of the racemic catalyst are ongoing, but only low to moderate enantioselectivities were detected in initially experiments. Also, chiral *R*- and *S*-configured BINOL complexes were employed in these reactions. No enantioselectivities were detected in these tranformations. Recently, other multinuclear chiral titanium clusters (e.g., a hexanuclear cluster with a chiral reactive cave) have been synthesized in our laboratories, and the catalytical properties will be explored.[23]

Conclusion

In summary, we have expanded our results concerning direct aldol additions. These reactions were promoted by extreme low loadings of air- and water-stable titanium catalyst **1**. The method in hand represents a valuable addition to kinetically controlled regioselectivities as they were observed in several other direct aldol additions to unsymmetrical methyl ketones. [24−31] For control of regioselectivity in aldol additions of trimethylsilyl enol ethers of unsymmetrical ketones depending on counterac-

(20) Calinoud, P.; Veyssieres-Rambaud, S. *Bull. Soc. Chim. Fr*. **1973**, 2769.

(21) Calculated structure of the protected aldol **22** (geometric optimization/SymApps). NOE effects are visualized with green arrows. See Supporting Information.



(22) (a) Keck, G. E.; Tabert, K. H. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (b) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc*. **1996**, *118*, 1217.

(23) Schetter, B.; Stosiek, C.; Ziemer, B.; Mahrwald, R. *Appl. Organomet. Chem*. **2007**, *21*, 139.

(24) Proline-catalyzed direct aldol additions: (a) Liu, H.; Peng, L.; Zhang, T.; Li, Y. *New J. Chem*. **2003**, *27*, 1159. (b) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett*. **2004**, *6*, 2285. (c) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J*. **2006**, *1*, 210. (d) Samanta, S.; Zhao, C.-G. *Tetrahedron Lett*. **2006**, *47*, 3383. (e) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2006**, *128*, 734. (f) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett*. **2007**, *9*, 1247. (g) Samanta, S.; Zhao, C.-G. *Tetrahedron Lett*. **2006**, *47*, 3383. (h) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2001**, *123*, 5260.

(25) Antibody-catalyzed direct aldol additions: (a) Baker-Glenn, C.; Ancliff, R.; Gouverneur, V. *Tetrahedron* **2004**, *60*, 7607. (b) Maggiotti, V.; Bahmanyar, S.; Reiter, M.; Resmini, M.; Houk, K. N.; Gouverneur, V. *Tetrahedron* **2004**, *60*, 619. (c) Maggiotti, V.; Wong, J.-B.; Razet, R.; Cowley, A. R.; Gouverneur, V. *Tetrahedron: Asymmetry* **2002**, *13*, 1789. (d) Maggiotti, V.; Resmini, M.; Gouverneur, V. *Angew. Chem., Int. Ed*. **2002**, *41*, 1012. (f) Tanaka, F.; Barbas, C. F., III. In *Modern Aldol Reactions*; Mahrwald, R., Ed.: Wiley-VCH: Weinheim 2004; Vol. 1, p 273.

(26) MgI_2-amine-promoted direct aldol addition: Wei, H.-X.; Jasoni, R. L.; Shao, H.; Hu, J. Paré, P. W. *Tetrahedron* **2004**, *60*, 11829.

(27) Bis(amido)magnesium-mediated aldol additions: Allan, J. F., Henderson, K. W., Kennedy, A. R. *Chem. Commun*. **1999**, 1325.

(28) Organoaluminium-promoted direct aldol condensations: (a) Tsuji, J.; Yamada, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett*. **1979**, *24*, 2257. (b) Tsuji, J.; Yamada, T.; Kaito, M.; Mandai, T. *Bull Chem. Soc. Jpn*. **1980**, *53*, 417.

(29) Aluminium oxide promoted aldol condensation: Nondek, L.; Malek, J. *Collect. Czech. Chem. Commun*. **1980**, *45*, 1812.

(30) Lithium enolates: Gaudemar, M. *C. R. Seances Acad. Sci., Ser. C* **1974**, *279*, 961.

(31) Similar results of kinetically controlled regioselectivities in organocatalyzed direct aldol additions depending on the bulkiness of unsymmetrical ketones used were reported by Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J*. **2006**, *1*, 210.

tions (lithium or potassium). see ref 32. The synthetical power of this reaction significantly exceeds that of the $TiCl_4$-mediated, since interesting results were obtained with oxygen-containing ene components. Further investigations aiming at an enantioselective execution are underway.

Experimental Section

3-Butyl-4-hydroxy-4-phenyl-butan-2-one (4a).[33] Benzaldehyde (636 mg, 6 mmol; 3 equiv) and heptan-2-one (228 mg, 2 mmol; 1 equiv) were mixed at room temperature, and 0.2 mol % of the calalyst was added. The procedure of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether and quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. Column chromatography (hexane/ethylacetate) afforded 299 mg (68%) pure aldols.

***syn*-4a.** Colorless oil. ^{1}H NMR: δ 0.69 (t, 7.2 Hz, 3 H, CH_3), 0.90−1.65 m, 6 H, $CH_2CH_2CH_2$), 1.83 (s, 3H, CH_3), 2.73 (dt, J_1 = 4.9 Hz, J_2 = 6.0 Hz, 1 H, CH), 4.69 (d, 6.0 Hz, 1 H, C*H*OH), 7.10−7.25 (m, 5 H, ar). ^{13}C NMR: δ 13.8, 22.8, 27.1, 29.9, 31.8, 59.6, 74.1, 126.1, 127.6, 128.4, 142.0, 213.2.

***anti*-4a.** Colorless oil. ^{1}H NMR: δ 0.74 (t, J = 7.2 Hz, 3 H, CH_3), 0.90−1.65 m, 6 H, $CH_2CH_2CH_2$), 1.83 (s, 3 H, CH_3), 2.33 (dt, $J_1 = J_2$ = 7.5 Hz, 1 H, CH), 4.99 (dd, J_1 = 4.2 Hz, J_2 = 8.7 Hz, 1 H, C*H*OH), 7.10−7.25 (m, 5 H, ar). ^{13}C NMR: δ 13.9, 22.4, 23.4, 29.9, 31.3, 43.7, 69.9, 125.6, 127.6, 128.4, 142.8, 211.7.

Large amounts of recovered ketone indicate the necessity to use longer reacion times or higher reaction temperatures in some cases, especially when the reactivity of the employed aldehydes or ketones was lower.

1,5-Dimethyl-3-phenyl-2,6,8-trioxa-bicyclo[3.2.1]octan-4-ol (16a). Hydroxyacetone (148 mg, 2 mmol; 1 equiv) and benzaldehyde (1060 mg, 10 mmol; 5 equiv) were mixed at room temperature, and 0.2 mol % of the calalyst was added. The procedure of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether and quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. Column chromatography (hexane/ethylacetate) afforded 158 mg (67%) pure aldols.

***syn*-16a.** Colorless solid. Mp = 70−71 °C. ^{1}H NMR: δ 1.56 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.85 (d, J = 9.0 Hz, 1 H, OH), 3.40 (dd, J_1 = 2.25 Hz, J_2 = 9.0 Hz, 1 H, CH), 3.76 (d, J = 8.3 Hz, 1 H, CH), 4.20 (d, J = 8.7 Hz, 1 H, CH), 5.16 (d, J = 2.6 Hz, 1 H, CH), 7.25−7.40 (m, 5 H, ar). ^{13}C NMR: δ 20.4, 20.7, 70.6, 72.0, 75.3, 104.4, 108.7, 126.1, 127.8, 128.4, 137.4. IR (KBr): 3478, 3058, 3034, 2905, 2357, 1244, 1226, 1187, 1088, 1075, 1037, 868. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.82; H, 6.99. MS (EI, relative intensity, %): 235.1 (0.5), 205.1 (1), 163.1 (6), 145.1 (9), 121.1 (26), 91.1 (100), 77.0 (20). HRMS (ESI) [$C_{13}H_{16}O_4$; M]$^+$: calcd 236.1049, found 236.1049.

***anti*-16a.** Colorless solid. Mp = 128−129 °C. ^{1}H NMR: δ 1.55 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 1.76 (d, J = 9.0 Hz, 1 H, OH), 3.25 (dd, $J_1 = J_2$ = 9.9 Hz, 1 H, CH), 3.81 (d, J = 8.3 Hz, 1 H, CH), 4.25 (d, J = 8.3 Hz, 1 H, CH), 4.54 (d, J = 8.3 Hz, 1 H, CH), 7.25−7.40 (m, 5 H, ar). ^{13}C NMR: δ 19.8, 20.4, 72.8, 74.1, 79.0, 104.4, 108.7, 127.2, 128.5, 138.4 (one aryl signal is hidden under the 127.2 or 128.5 signal). IR (KBr): 3486, 3446, 3064, 3034, 2944, 2905, 2894, 1452, 1383, 1248, 1228, 1206, 1186, 1144, 1098, 1076, 1045, 1012, 915, 903, 848, 797, 755, 702. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.04; H, 6.82. MS (EI, relative intensity, %): 205.1 (0.5), 163.1 (3), 145.1 (10), 121.1 (42), 91.1 (100), 77.0 (18). HRMS (ESI) [$C_{13}H_{16}O_4$; M]$^+$: calcd 236.1049, found 236.1049.

1-(2,4-Dimethyl-[1,3]dioxolan-4-yloxy)-propan-2-one (19a).[20] Hydroxyacetone (148 mg, 2 mmol;1 equiv) and acetaldehyde (352 mg, 8 mmol; 4 equiv) were mixed at room temperature, 0.2 mol % of the calalyst was added, and the mixture cooled to avoid evaporation of acetaldehyde. The procedure of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether and quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. Column chromatography (hexane/ethylacetate) afforded 50 mg (32%) pure acetals.

Major. ^{1}H NMR: δ 1.30 (d, J = 4.91, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 3.81 (d, J = 8.5 Hz, 1 H, CH), 3.91 (d, J = 8.7 Hz, 1 H, CH), 4.04 (d, J = 16.8 Hz, 1 H, CH), 4.14 (d, J = 17.0 Hz, 1 H, CH), 5.19 (q, J = 4.91 Hz, 1 H, CH). ^{13}C NMR: δ 19.4, 21.3, 26.5, 68.1, 76.3, 101.3, 105.4, 206.4.

Minor. ^{1}H NMR: δ 1.37 (d, J = 4.91, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 3.58 (d, J = 9.44 Hz, 1 H, CH), 4.01 (d, J = 17.0 Hz, 1 H, CH), 4.06 (d, J = 7.4 Hz, 1 H, CH), 4.11 (d, J = 16.4 Hz, 1 H, CH), 5.05 (q, J = 4.91 Hz, 1 H, CH). ^{13}C NMR: δ 19.5, 22.7, 26.7, 68.3, 74.9, 102.6, 105.1, 207.4. IR (KBr): 2991, 2937, 2892, 1733, 1717, 1446, 1411, 1381, 1356, 1230, 1175, 1144, 1112, 1097, 895. MS (EI, relative intensity, %). 157.1 (5), 133.1 (9), 115.1 (16), 101.1 (84), 57.0 (54), 43.0 (100). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.12; H, 8.04. HRMS (ESI) [$C_8H_{14}O_4Na$; M + Na]$^+$: calcd 197.0784, found 197.0785.

1,4,7-Trimethyl-3,5,9,10-tetraoxa-tricyclo[5.2.1.0^{4,8}]decane (22). Hydroxyacetone (148 mg, 2 mmol) was mixed with 0.2 mol % of the catalyst at room temperature. The progress of the reaction was monitored by TLC, and when the turnover was complete, the reaction mixture was diluted with diethyl ether and quenched with aqueous NH_4Cl. The organic layer was separated, dried ($MgSO_4$), and filtered, and the ether was removed in vacuo. Column chromatography (hexane/ethylacetate) afforded 67 mg (54%) pure aldol. Colorless solid, mp 40−41 °C. ^{1}H NMR: δ 1.29 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 3.57 (d, J = 10.9 Hz, 1 H, CH_2), 3.62 (d, J = 10.2 Hz, 1 H, CH_2), 3.63 (d, J = 11.3 Hz, 1 H, CH_2), 4.05 (d, J = 10.2 Hz, 1 H, CH_2), 4.06 (s, 1 H, CH). ^{13}C NMR: δ 20.6, 22.1, 24.8, 69.4, 74.8, 85.1, 86.2, 102.9, 105.5. IR (KBr): 2985, 2935, 2876, 1449, 1382, 1293, 1253, 1172, 1126, 1096, 1079, 1039, 903, 885, 836. MS (EI, relative intensity, %): 186.1 (0.5) 156.1 (8), 141.1 (2), 114.1 (4), 97.1 (100), 85.0 (7), 43.0 (49). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.49; H, 7.33. HRMS (ESI) [$C_9H_{14}O_4$; M]$^+$: calcd 186.0892, found 186.0892.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, Konrad-Adenauer-Stiftung and Bayer Schering Pharma AG, Bayer Services GmbH, BASF AG and Sasol GmbH. Enantiopure BINOL was a gift of Merck KGaA, Darmstadt, Germany. Petra Neubauer is grateful acknowledged for technical support.

Supporting Information Available: General experimental procedures, characterization data, and NMR spectra for all new compounds and X-ray crystal data in CIF format for compounds **1**, **6**, *syn*-**9d**, *syn*-**16a**, and *anti*-**16a** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7014054

(32) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232.

(33) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, *19*, 1665.