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On the mechanism of directed, $TiCl_4$-mediated aldol addition—an easy access to substituted 2.4-furandiols

R. Mahrwald,* B. Ziemer and S. Troyanov

Institut für Organische und Bioorganische Chemie der Humboldt Universität, Hessische Str. 1-2, D-10115 Berlin, Germany

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Abstract—Different results of directed $TiCl_4$-mediated aldol additions in the presence of bases as well as in the absence of bases followed by an α-hydroxylation were obtained. © 2001 Published by Elsevier Science Ltd.

Recently we described a directed, $TiCl_4$-mediated aldol addition of aldehydes and ketones. Surprisingly, unactivated carbonyl compounds react in the presence of substoichiometric amounts of $TiCl_4$ and in the absence of bases to give *syn*-aldol adducts with a high degree of stereoselectivity[1] and regioselectivity.[2] In conjunction with our ongoing studies of this directed *Lewis*-acid mediated aldol process, the question arose as to whether or not enolates are involved during this reaction. As has been previously described, no hint of enolate participation during the reaction has been observed.[1]

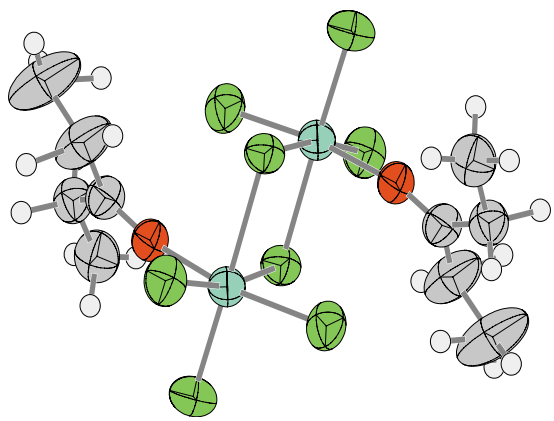
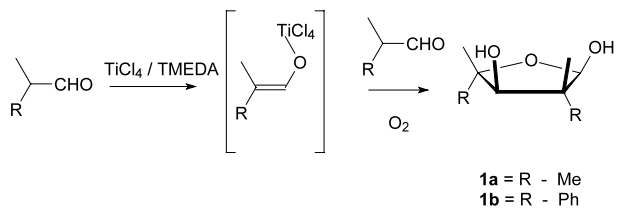


Figure 1.



Scheme 1.

The NMR analysis of a solution of a $TiCl_4$–diethyl ketone complex also does not detect the presence of enolates. Only low-field shift of the signals of diethyl ketone were observed.[3] An X-ray analysis of the $TiCl_4$–diethyl ketone complex resulted in the dimeric structure shown in Fig. 1. There was no evidence of shortened C–C bonds or of so-called agostic hydrogen atoms (elongated α-C–H bonds in organometallics).

For this reason, chemical trapping for any short-lived enolates that may be formed during the aldol reaction was proposed. The α-hydroxylation of enolates seemed to be a suitable reaction for providing α-hydroxy carbonyl compounds.[4] For that purpose, we investigated the $TiCl_4$-mediated self aldol addition of 2-phenylpropionaldehyde[5]—an enolate stabilizing carbonyl compound—followed by an α-hydroxylation. For comparison, the $TiCl_4$-mediated aldol addition in the presence of bases[6] as well as the $TiCl_4$-mediated aldol addition in the absence of base followed by an α-hydroxylation were performed.

First, 2-phenylpropionaldehyde was reacted with equimolar amounts of $TiCl_4$ in the presence of TMEDA at room temperature. After 2 h the reaction was treated with dry oxygen. Work up of the reaction mixture yielded the acetal **1b** (Scheme 1).[7] Structure and configuration of the compound was confirmed by X-ray

Keywords: aldol addition; α-hydroxylation; catalysis.

* Corresponding author. Tel.: +49-30-2093 8397; fax: +49-30-2093 8479.

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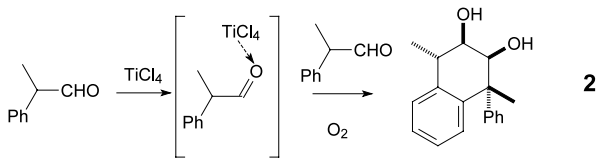

Scheme 2.

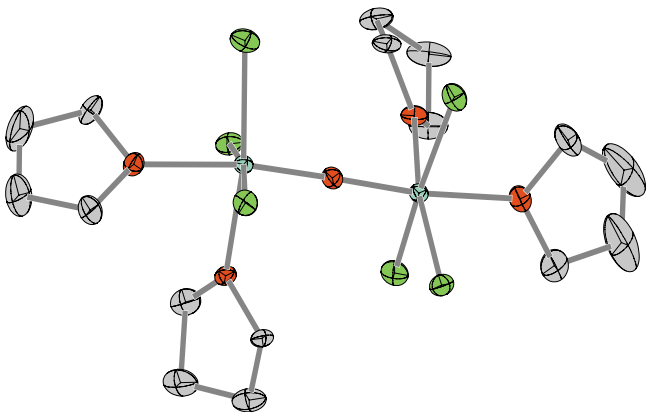

Figure 2.

analysis. During the aldol addition, the desired α-hydroxylation took place and subsequently the corresponding acetal was formed with a high degree of stereoselectivity. No other isomers were detected.

The reaction sequence can be extended to those other α-branched aldehydes, which are capable of forming and stabilizing enolates. Corresponding acetals **1a** were obtained from *iso*-butyraldehyde. No reactions were observed with *n*-aliphatic aldehydes. Thus, this reaction sequence represents an easy approach to substituted 2.4-furandiols. Yields are not optimized.

In contrast to other results that were obtained by $TiCl_4$-mediated aldol addition in the absence of base, 2-phenylpropionaldehyde was reacted with equimolar amounts of $TiCl_4$ at room temperature. After 2 h the reaction was treated with dry oxygen and work up of the reaction mixture yielded diol **2**.[8] Structure and configuration were confirmed by X-ray analysis. The formation of this unexpected compound may be explained by a *McMurry* pinacol coupling process[9] followed or accompanied by an aromatic *ortho*-substitution (Scheme 2).

The exact reaction mechanism is not clear at this time. But strong evidence for low valent titanium species and consequently for a *McMurry* type pinacol coupling process were observed with similar aldol process performed in THF in which the titanium complex $TiCl_3(THF)_2$–*O*-$TiCl_3(THF)_2$ was isolated and subsequently characterized by X-ray analysis. The structure of this complex is shown in Fig. 2.

It is important to keep in mind that the products isolated were found only from their individual reaction conditions. Acetals **1a** and **1b** are only found in the $TiCl_4$-mediated aldol alddition in the presence of bases while the diol **2** is not detected in the presence of base. The results from two different aldol procedures, one in the presence of base and the other one in the absence of base, suggests two completely different reaction pathways. Further investigations are in progress.

Crystal structures have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition numbers CCDC 167138 (Fig. 1), CCDC 167139 (**1b**), CCDC 167140 (**2**), CCDC 167141 (Fig. 2).

Acknowledgements

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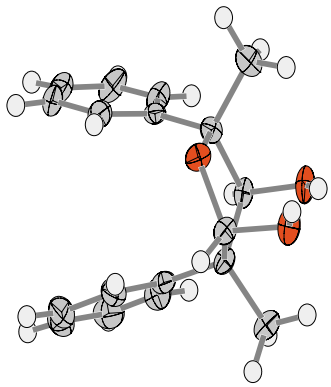
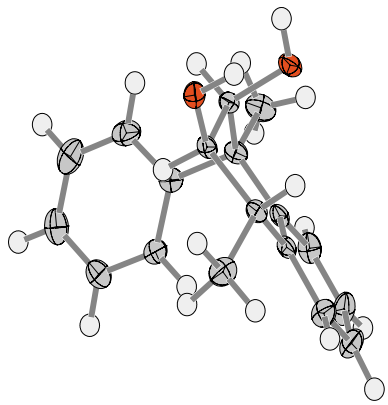
7. **rac - 3(*R*),5(*S*) - Dimethyl - 3,5 - diphenyl - tetrahydrofuran-2(*S*),4(*R*)-diol (1b):** 1.5 ml TMEDA (10 mmol) were added to 660 µl 2-phenylpropionaldehyde (5 mmol) in 1.0 ml dichloromethane. 1.1 ml (10 mmol) $TiCl_4$ was added to that solution carefully under cooling. The deep dark brown solution was stirred for 24 h at room temperature. The reaction solution was extracted between diethylether and aq. sat. $NaHCO_3$ solution. The organic layers were collected, dried (Na_2SO_4), filtrated and evaporated in vacuo. The oily residue was purified by column chromatography (hexane/ethylacetate 8/2). Crystallization in toluene gave 150 mg diol **1b** (22.1% yield).
Mp 165–169°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05–7.38 (m, 10H), 5.72 (d, 1H, J=6.8 Hz, C-1), 5.28 (d, 1H, J=6.9 Hz, -OH), 4.68 (d, 1H, J=7.2 Hz, C-3), 4.38 (d, 1H, J=7.2 Hz, -OH), 1.42 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 147.3, 128.3, 127.2, 126.4, 126.2, 124.3, 124.1, 101.2, 85.4, 82.0, 52.3, 27.7, 18.3.



X-ray structure of **1b**

8. **rac - 1,2,3,4 - Tetrahydro - 1(*R*),4(*S*) - dimethyl - 1 - phenyl-2(*R*),3(*R*)-naphtalene-diol (2)**: 1.1 ml $TiCl_4$ (10 mmol) were carefully added to a stirred solution of 1.33 ml 2-phenyl-propionaldehyde (10 mmol) in 2 ml abs. dichloromethane. The resulting orange–brown solution was stirred for 24 h at room temperature. The reaction solution was extracted between diethylether and aq. sat. $NaHCO_3$-solution. The organic layers were collected, dried (Na_2SO_4), filtrated and evaporated in vacuo. The oily residue was purified by column chromatography (hexan/ethylacetate 8/2). Crystallization in water yielded 250 mg **2** (18.7% yield).

Mp 85–87°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.9–7.3 (m, 10H), 4.0 (d, 1H, $J=2.1$ Hz), 3.3 (dd, 1H, $J=2.2$, 8.7 Hz), 2.9 (dq, 1H, $J=6.9$, 8.8 Hz), 1.8 (s, 3H), 1.3 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.7, 140.2, 138.8, 128.6, 128.1, 127.4, 127.3, 126.9, 126.6, 126.1, 79.2, 72.4, 48.6, 37.3, 26.2.



X-ray structure of **2**

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