CHEMCOMM Communication
www.rsc.org/chemcomm

$Zr(OtBu)_4$-catalysed synthesis of acetone aldol adducts and domino aldol-Tishchenko reactions with diacetone alcohol as enol equivalent†

Christoph Schneider* and Markus Hansch

Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstr. 2, D-37077 Göttingen, Germany. E-mail: cschnei1@gwdg.de; Fax: (+ 49)551-399660

Received (in Cambridge, UK) 2nd April 2001, Accepted 16th May 2001
First published as an Advance Article on the web 14th June 2001

$Zr(OtBu)_4$ was found to be a potent catalyst for the synthesis of acetone aldol adducts with diacetone alcohol as enol equivalent and for domino aldol-Tishchenko reaction giving rise to 1,3-*anti*-diol monoesters with excellent diastereoselectivity.

Catalytic aldol reactions are currently being intensely investigated. Most processes that have been developed share as a general feature the formation of a silyl enolate in a preceding synthetic operation which in a separate step is then treated with the aldehyde under Lewis acid[1] or Lewis base[2] catalysis. Only very recently few methods for direct, catalytic aldol reactions have been reported.[3] Typically these catalysts exhibit Brønsted base as well as Lewis acid activity to form the metal enolate *in situ* and activate the aldehyde, respectively.

Recently, pharmaceutical chemists aiming at modifying the chemical structure of the immunosuppressant rapamycin reported that the homogeneous stereochemistry of the aldol moiety of the natural product was lost under the action of excess $Ti(OiPr)_4$.[4] They proposed a facile retro-aldol aldolisation process to account for this observation and pointed to the possible use of aldol products as enolate precursors. Inspired by this report we reasoned that a ketone aldol adduct should be an even better source for the *in situ* generation of a metal enolate through a retro-aldol mechanism and selected diacetone alcohol (**1**) as a promising substrate for a direct and catalytic aldol synthesis.[5]

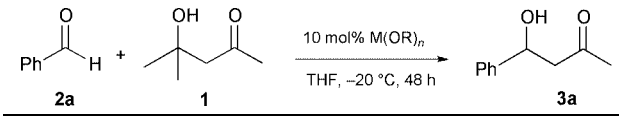
We report here that $Zr(OtBu)_4$ catalyses the synthesis of aldol products from aromatic and α,β-unsaturated aldehydes **2** and diacetone alcohol (**1**) to give rise to the acetone aldol products **3** in typically good yields. Moreover, with most aliphatic aldehydes a rapid $Zr(OtBu)_4$-catalysed Tishchenko reduction of the β-hydroxyketones immediately succeeds the aldol reaction to yield the 1,3-*anti*-diol monoesters **4**/**5**.

In the first step various metal alkoxides (10 mol%) were tested for their catalytic activity in the reaction of benzaldehyde and diacetone alcohol in THF at −20 °C (Table 1). NaO*t*Bu and KO*t*Bu apparently catalysed the reaction but yielded mainly the dehydrated aldol condensation product (entries 1, 2). $Ti(OiPr)_4$ and $Ti(OtBu)_4$ required elevated temperatures for product formation and gave mixtures of **3a** and the condensation product in moderate yields (entries 3, 4). Whereas $Zr(OiPr)_4$ also exhibited poor catalytic activity, $Zr(OtBu)_4$[6] turned out to be the catalyst of choice furnishing the desired aldol adduct **3a** in 80% yield with only traces of the condensation product being formed (entry 6). $La(OtBu)_3$ yielded mainly the direct aldol adduct of diacetone alcohol and benzaldehyde as one might have expected in light of the results reported by Shibasaki (entry 7).[3]

We then subjected a range of aromatic and conjugated aldehydes to the reaction with diacetone alcohol (2 eq.) and $Zr(OtBu)_4$ (10 mol%) in THF at −20 °C which gave rise to the corresponding aldol adducts **3a**–**f** in moderate to very good yields (Table 2).[7] Not unexpectedly, electron-deficient aromatic aldehydes appear to be slightly more reactive than electron-rich ones (entries 2, 3). As byproduct in 5–10% yield we occasionally isolated 1,3-*anti*-diol monoesters comprising two molecules of aldehyde and one acetone fragment which were apparently formed in a $Zr(OtBu)_4$-catalysed Tishchenko reduction[8] of the initially formed β-hydroxy ketones with the aldehyde as hydride source.

This domino aldol-Tishchenko process[9,10] was found to be the dominant reaction pathway in the case of most aliphatic aldehydes (Table 3). Straight chain as well as α-branched aliphatic aldehydes gave the 1,3-*anti*-diol monoesters **4**/**5a**–**e** in good yields upon reaction with diacetone alcohol (1 eq.) and $Zr(OtBu)_4$ (10 mol%) whereas the initial aldol adducts were isolated in < 5% yield. Lowering the amount of aldehyde equivalents resulted in a decrease in yield but did not increase the proportion of the aldol adducts, indicating that the Tishchenko reduction proceeded much faster than the formation of the aldol adducts. Only pivalaldehyde as a sterically very hindered aliphatic aldehyde yielded mainly the initial aldol

Table 1 Metal alkoxide-catalysed synthesis of acetone aldol adduct **3a**

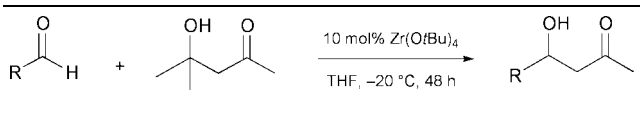


2a **1** **3a**

Entry	Metal alkoxide	Yield of **3a** [%][a]
1	NaO*t*Bu	23 (35)
2	KO*t*Bu	17 (49)
3	$Ti(OiPr)_4$[b]	20 (16)
4	$Ti(OtBu)_4$[b]	35 (28)
5	$Zr(OiPr)_4$	14 (0)
6	$Zr(OtBu)_4$	80 (2)
7	$La(OtBu)_3$	15[c]

[a] Yield of dehydrated aldol condensation product in brackets. [b] This reaction was run at rt. [c] In addition the 'direct' aldol product was formed in 46% yield.

Table 2 $Zr(OtBu)_4$-catalysed synthesis of acetone aldol adducts **3**



2 **1** **3**

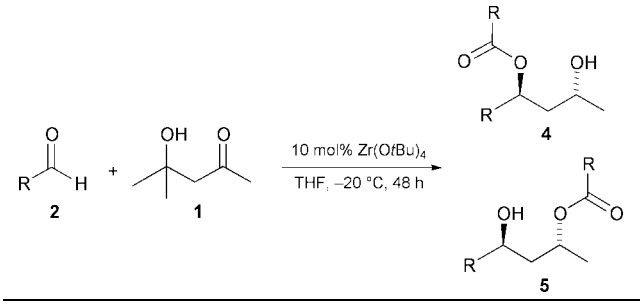
Entry	RCHO	Aldol **3**	Yield [%][a]
1	Ph	**3a**	80
2	4-NO_2-Ph	**3b**	85
3	4-MeO-Ph	**3c**	68
4	1-naphthyl	**3d**	86
5	2-naphthyl	**3e**	71
6	PhCH=CH	**3f**	60
7	*t*Bu	**3g**	60

[a] 5–10% of the corresponding aldol Tishchenko products were formed additionally.

† Dedicated to Professor David A. Evans on the occasion of his 60th birthday.

 DOI: 10.1039/b102941j

Table 3 $Zr(OtBu)_4$-catalysed domino aldol-Tishchenko reactions

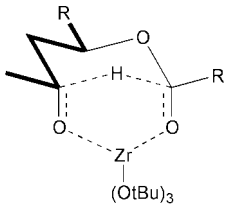


Entry	RCHO	4/5	Yield [%][a]
1	C_2H_5	**4/5a** (3:1)	75
2	nC_6H_{13}	**4/5b** (2:1)	89
3	$PhCH_2CH_2$	**4/5c** (1:1)	75
4	iC_3H_7	**4/5d** (9:1)	85
5	cC_6H_{11}	**4/5e** (22:1)	70

[a] Combined yield of both regioisomers; the initial aldol products were formed in < 5% yield.

adduct **3g** in 60% yield along with 6% of the aldol Tishchenko product (Table 2, entry 7).

The initial Tishchenko products **4** suffered partial acyl migration to give rise to mixtures of regioisomeric 1,3-*anti*-diol monoesters which were, however, converted to a single 1,3-*anti*-diol upon hydrolysis with KOH in methanol. ^{13}C NMR analysis of the corresponding acetonides confirmed their *anti*-stereochemistry.[11] The degree of acyl migration was dependent on the steric bulk of the acyl group with straight-chain acyl groups being more readily transferred than α-branched acyl groups. The exclusive (> 97:3 by NMR) formation of the 1,3-*anti*-diol monoesters may be explained through intramolecular hydride delivery of a chelated Zr-hemiacetal alkoxide in transition structure **A** which has been previously put forth for transition metal-catalysed Tishchenko reductions (Fig. 1).[8]

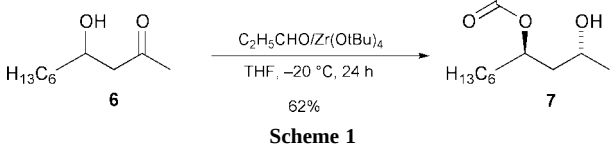


A

Fig. 1

In an additional experiment we treated aldol adduct **6** with propionaldehyde under the typical reaction conditions and obtained the Tishchenko product **7** in 62% yield (15:1-mixture of regioisomers) with no formation of a crossover product being observed (Scheme 1). This result suggests that the Tishchenko reduction proceeded faster than a possible retro-aldol aldolisation process.

At present, we can only speculate about the exact mechanism of the reported aldol synthesis. Although it is very likely that the reaction proceeds stepwise *via* a retro-aldol aldolisation pathway and *in situ* generation of a zirconium enolate, we can not rule out a concerted mechanism analogous to a Meerwein–Ponndorf–Verley reduction.[12] Attempts to detect the presumed zirconium enolate spectroscopically have failed so far which, however, may be due to the very low concentration of the enolate that reacts with the aldehyde as soon as it is formed.



Scheme 1

In conclusion, we have demonstrated that $Zr(OtBu)_4$ is an effective catalyst for the synthesis of acetone aldol adducts using diacetone alcohol as an enol equivalent. With most aliphatic aldehydes $Zr(OtBu)_4$ exhibits a dual activity as an aldol and Tishchenko catalyst. Further studies are aimed at understanding the exact reaction mechanism and expanding the scope of the reaction.

Financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Professor Tietze for his support.

Notes and references

1 For excellent reviews see: E. M. Carreira, in *Comprehensive Asymmetric Catalysis*, eds. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Heidelberg, 1999, vol. **3**, p. 998; H. Gröger, E. M. Vogel and M. Shibasaki, *Chem. Eur. J.*, 1998, **4**, 1137; S. G. Nelson, *Tetrahedron: Asymmetry*, 1998, **9**, 357.

2 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432 and ref. cited; S. Matsukawa, N. Okano and T. Imamoto, *Tetrahedron Lett.*, 2000, **41**, 103.

3 N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 4168; B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395; B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12003; N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 2466.

4 W. Yang, C. A. Digits, M. Hatada, S. Narula, L. W. Rozamus, C. M. Huestis, J. Wong, D. Dalgarno and D. A. Holt, *Org. Lett.*, 1999, **1**, 2033.

5 While this work was in progress Nevalainen *et al.* reported a Al-catalysed aldol synthesis based on the same concept, see: I. Simpura and V. Nevalainen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3422.

6 H. Sasai, Y. Kirio and M. Shibasaki, *J. Org. Chem.*, 1990, **55**, 5306.

7 Typical experimental procedure for the aldol synthesis: in a dry flask under nitrogen 0.10 ml (1.00 mmol) freshly distilled benzaldehyde and 0.25 ml (2.00 mmol) of diacetone alcohol were dissolved in 1 ml THF and cooled to −20 °C. At that temperature 39 μl (0.10 mmol) $Zr(OtBu)_4$ were added with a syringe and the reaction mixture remained at −20 °C for 48 h. The reaction was quenched with pH 7 buffer, the product was extracted twice with ether and the organic extracts were dried with $MgSO_4$. Flash chromatography over silica gel with ether–pentane 1:2 furnished 132 mg (80%) of aldol adduct **3a** as a colourless oil along with 18 mg (7%) of the corresponding Tishchenko product. All products gave satisfactory analytical and spectroscopic data.

8 For metal-catalysed Tishchenko reductions of β-hydroxy ketones see: D. A. Evans and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1990, **112**, 6447; T. Ooi, T. Miura, K. Takaya and K. Maruoka, *Tetrahedron Lett.*, 1999, **40**, 7696.

9 For other stoichiometric aldol Tishchenko reactions see: E. R. Burckhardt, R. G. Bergman and C. H. Heatchcock, *Organometallics*, 1990, **9**, 30; D. P. Curran and R. L. Wolin, *Synlett*, 1991, 317; A. Baramee, N. Chaichit, P. Intawee, C. Thebtaranonth and Y. Thebtaranonth, *J. Chem. Soc., Chem. Commun.*, 1991, 1016; Y. Horiuchi, M. Taniguchi, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, 1995, **36**, 5353; P. M. Bodnar, J. T. Shaw and K. A. Woerpel, *J. Org. Chem.*, 1997, **62**, 5674; F. Abu-Hasanayn and A. Streitwieser, *J. Org. Chem.*, 1998, **63**, 2954.

10 For other catalytic aldol Tishchenko reactions see: R. Mahrwald and B. Costisella, *Synthesis*, 1996, 1087; L. Lu, H. Y. Chang and J. M. Fang, *J. Org. Chem.*, 1999, **64**, 843; C. M. Mascarenhas. M. O. Duffey, S. Y. Liu and J. P. Morken, *Org. Lett.*, 1999, **1**, 1427; C. Delas and C. Moise, *Synthesis*, 2000, 251; C. Mascarenhas, S. P. Miller, P. S. White and J. P. Morken, *Angew. Chem., Int. Ed.*, 2001, **40**, 601.

11 S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res.*, 1998, **31**, 9.

12 Maruoka *et al.* have reported Meerwein–Ponndorf–Verley alkynylations and cyanations of aldehydes, see: T. Ooi, T. Miura and K. Maruoka, *J. Am. Chem. Soc.*, 1998, **120**, 10790; T. Ooi, K. Takaya, T. Miura and K. Maruoka, *Synlett*, 2000, 69; T. Ooi, K. Takaya, T. Miura, H. Ichikawa and K. Maruoka, *Synlett*, 2000, 1133.