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Monoalcoholates of 1,3-diols as effective catalysts in the Tishchenko esterification of 1,3-dioxan-4-ols

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Abstract—Alkali metal monoalcoholates of 1,3-diols can be used as very effective catalysts in the Tishchenko reaction of 4-hydroxy-1,3-dioxanes to the corresponding monoesters of 1,3-diols. These catalysts are extremely efficient and fast compared to metal hydroxides commonly used. Thus, monoalcoholate catalysts give fast transesterification with the product ester. The loss in yield due to ester interchange can be minimized by using a suitable 1,3-diol moiety in the catalyst. © 2001 Published by Elsevier Science Ltd.

In the normal Tishchenko reaction two aldehydes are converted to a monofunctional simple ester in the presence of a Lewis acid catalyst,[1] most commonly with aluminium alcoholates.[2] The reaction has been carried out with a number of other catalysts such as ruthenium complexes,[3] alkali earth metal oxides,[4] boric acid,[5] sodium alkoxides[6] (with aryl aldehydes), alkali metals,[7] zirconocenes,[8] and lanthanide (amide) complexes.[9] The mechanism of the Tishchenko reaction involves a hydride shift.[2] Very recently a bidentate bisaluminum alcoholate has been reported to give an especially fast Tishchenko reaction with excellent yield.[10] One special case of the Tishchenko reaction is the esterification of 1,3-dioxan-4-ols where an intramolecular hydride shift is activated in the presence of a base catalyst. These dioxanols are usually dimers of β-hydroxyaldehydes (aldol product) or similar hemiacetals formed between β-hydroxyaldehydes and another aldehyde.[11] Merger et al. have reported the first mechanistic features of the esterification of such compounds (Scheme 1).[12] Esterification of 1,3-dioxan-4-ols is usually carried out with basic catalysts such as alkali metal hydroxides instead of the aluminium alcoholates used in the traditional Tishchenko reaction.[12]
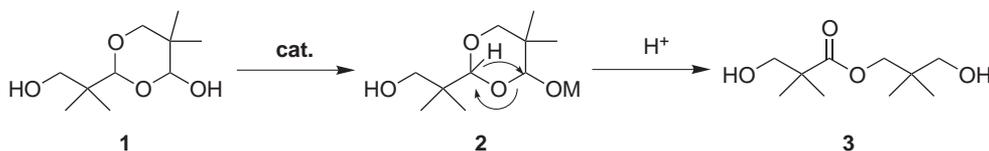
Scheme 1.
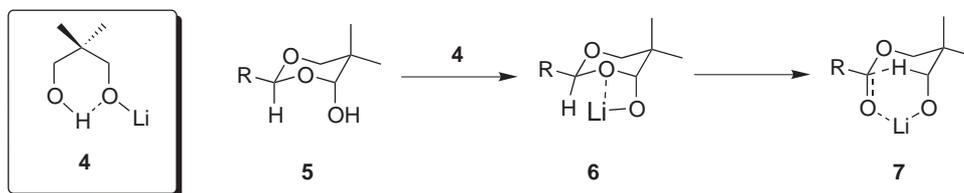
Scheme 2.

We have recently investigated the preparation and Tishchenko esterification of 4-hydroxy-1,3-dioxanols. Based on the literature and partly on our own previous work, the catalysts used in this case are usually metal hydroxides or alcoholates of monofunctional alcohols.[12,13] Metal hydroxides cause rapid and irreversible hydrolysis of product esters when used in catalytic amounts. Similarities in the mechanisms of hydrolysis and transesterification prompted us to use monoalcoholates of 1,3-diols as catalysts.

We report herein, for the first time to our knowledge, the use of monoalkalimetal alcoholates of 1,3-diols as very efficient and simple catalysts in the Tishchenko esterification of 1,3-dioxan-4-ols. To our surprise, the reaction was several times faster than with the metal hydroxides traditionally used. With these new 1,3-diol based catalysts such as 4 (Scheme 2), the hydrolysis of the product esters can be completely avoided but they seemed to give rapid transesterification between the product and the alcoholate catalyst. This limits the use of different diols, being case dependent (relative to structure of the used β-hydroxyaldehyde). The use of the catalyst was also found to be possible on larger scales.

In our catalyst experiments the 5,5-dimethyl-2-(1′,1′-dimethyl-2′-hydroxyethyl)-4-hydroxy-1,3-dioxane 1 (later referred to as dimeric HPA) was used as a test because of its good stability to storage and easy monitoring of the reactions. Compound 1 was prepared by the aldol reaction of 37% formalin and 2-methylpropanal in the presence of Et_3N catalyst with 86% yield.[14] The aldol product spontaneously dimerized and precipitated to give dioxanol 1 as a mixture of diastereomers with a ratio of 40:60 when cooled to room temperature. An apolar solvent (i-octane) was used to facilitate the dimerization. Initially, different metal hydroxides were used as catalysts in order to study the effects of the metal on the rate of esterification to monoester 3 and hydrolysis. In all experiments 5 mol% of the catalyst was used.

Alkali metal hydroxides gave faster esterification than alkali earth metal hydroxides, but rapid hydrolysis of 3 was observed in every case. Some results of these experiments are collected in Table 1. Unfortunately, metal hydroxides usually require the presence of water that may require extra investment, e.g. in handling waste water on an industrial scale. Another problem is the stability of 1,3-dioxan-4-ols in the presence of

water. Dioxanols related to HPA 1 are hemiacetal like dimers of β-hydroxyaldehydes, which can be monomerized in the presence of water and with slight heating. Thus, the monomerization of 1,3-dioxan-4-ols, due to the presence of water, can partly interfere with their Tishchenko esterification to monoesters.

$Al(O^iPr)_3$ was found to be inactive as a catalyst. It is possible that catalytic aluminium coordinates to the primary hydroxyl group located at the end of the side chain of 1 instead of forming the transition state related to 6. Lanthanide oxides (e.g. Nd_2O_3) also gave negative results. The reaction proceeds only in the presence of basic catalysts indicating that deprotonation is an initial step of the reaction.

In order to avoid hydrolysis we reasoned that use of a monoalcoholate of the diol as the catalyst might solve the problem. Additionally, the product from transesterification is the same if the 1,3-diol in the catalyst is the same as in the monoester product after Tishchenko esterification. Meth-Cohn has reported that lithium alcoholates give quite fast transesterification with an ester when THF was used as the solvent.[15] To our surprise such catalysts gave reactions (1→3) several times faster than the metal hydroxides we had tested previously. The first diol based catalyst we studied was monolithium-2,2-dimethyl-1,3-propandiol 4 (later Li-NPG; neopentyl glycol).[16] With catalyst 4 (5 mol%) the reaction was complete in 25 minutes even at 0°C and monoester 3 was obtained in 92% isolated yield. The reaction was quenched with a slight excess of 2 M HCl in order to avoid the presence of LiOH and hydrolysis of the product. The efficiency of catalyst 4 is most likely due to its good solubility in organic solvents which provides totally homogenous reaction conditions. In contrast, with metal hydroxides these reactions are usually two phase systems (especially with higher aldehydes) or a totally heterogeneous slurry ($Ca(OH)_2$). Another reason for the efficiency of the catalyst might be intramolecular hydrogen bonding in the catalyst 4, which could lead to an increased cationic nature of the metal and thus give easier and stronger coordination to the substrate 1 (Scheme 2). The mechanism has been discussed very briefly earlier (as presented here in Scheme 1) by Merger et al.[12] We believe that the catalyst first deprotonates a hydroxyl group of the dioxanol ring and then coordinates to the hydroxyl group and the ring oxygen in position 2 of the dioxanol 5. The electron density will be shifted from both oxygens and the carbon between them towards lithium (6

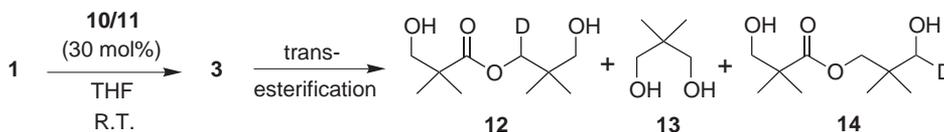**Table 1.** Some catalyst tests in the Tishchenko esterification of 1,3-dioxan-4-ol 1 to monoester 3

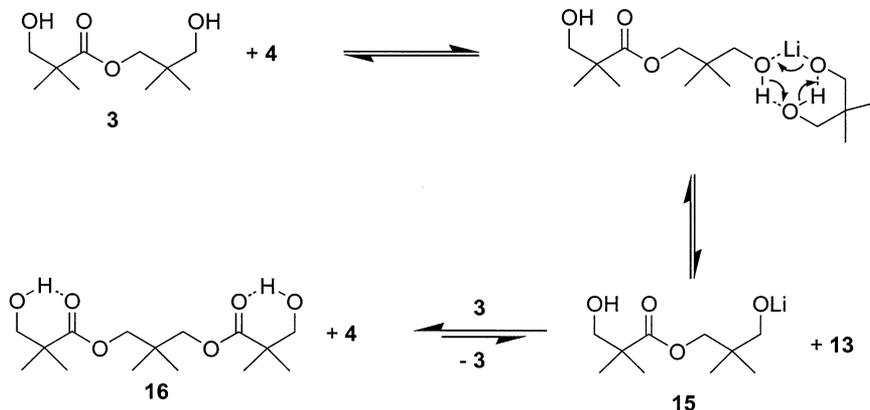| Entry	Catalyst	Solvent	T (°C)	Reaction time	Yield (%)[a]
1	LiOH (4.5 M)	MTBE	+32	6 hours	70
2	$Ca(OH)_2$ (neat)	MTBE	+32	Days	65
3	$Ba(OH)_2 \times 8H_2O$	MTBE	+32	40 min	88
4	$Al(O^iPr)_3$	MTBE	+32	No reaction	0
5	Nd_2O_3	MTBE	+32	No reaction	0
6	Li-NPG (4)	THF	0	25 min	92

[a] Isolated yield.
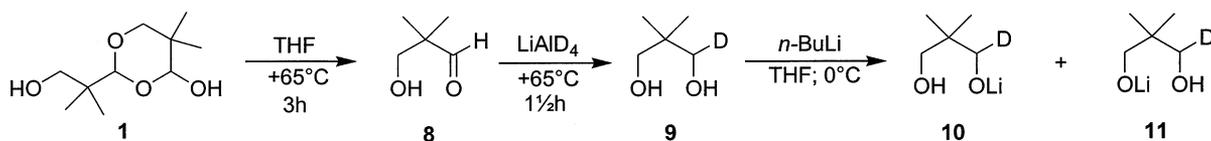
Scheme 3.

Scheme 4.

Scheme 5.

in Scheme 2). This coordination opens the dioxanol ring and facilitates a hydride shift via a chair like [6,6]-membered bicyclic transition state **7**, in analogy to a Tishchenko esterification between a β-hydroxyketone and an aldehyde first reported by Evans et al.[17]

Transesterification between the catalyst and the product ester was established using deuterium labelled mono-lithio-2,2-dimethyl-1,3-propanediol catalysts **10** and **11** (Scheme 4). In order to prepare **9**, dimeric HPA **1** was monomerized by heating in THF at +65°C for 3 hours under argon and the resulting monomer **7** was reduced with LiAlD$_4$ to **9** with 70% isolated yield (>99.5% deuterated) (Scheme 3).[18,19] Preparation of catalysts **10** and **11** was carried out with treatment of *n*-BuLi in THF at 0°C. The concentration of the catalyst used was usually 0.1 M in THF.

In the Tishchenko esterification of dimeric HPA **1** with 30 mol% of catalysts **10** and **11** the reaction was complete in less than 30 minutes at 0°C. GC–MS analysis showed that there were esters **3** and **12/14** in the ratio of 1:1 (Scheme 4). The reaction rate (**1**→**3**) was the same with both isotopic catalysts **4** and **10**. The product ester **3** rapidly transesterifies with the catalyst to form deuterated products **12** and **14**, as shown by NMR and MS.

If the reaction time of **3** and **1** was extended or an elevated reaction temperature was utilized, slow forma-

tion of diester **16** was observed. After a reaction time of 24 hours at room temperature (+25°C), **16** was the main product. The similar acidity of the primary hydroxyl groups in **3** and **13** allows lithium exchange between the catalyst and product ester (Scheme 5) to produce the alcoholate **15**. The preferred formation of **16** is probably due to stabilizing intramolecular hydrogen bonding which makes the protons less acidic and the diester more stable. The formation of **16** was also observed when pure monoester **3** was treated with the catalyst **4**.

In conclusion, utilization of monoalcoholates of 1,3-diols as catalysts allows Tishchenko esterification of 1,3-dioxan-4-ols to be carried out rapidly at low temperatures with good to excellent yields. Simultaneously, the product ester is not lost via hydrolysis (as with metal hydroxides) or ester interchange (as with alcoholates) when the proper 1,3-diol is used as the catalyst.

References

1. Lin, I.; Day, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 5133–5135.
2. Ogata, Y.; Kawasaki, A.; Kishi, I. *Tetrahedron* **1967**, *23*, 825–830.
3. Ito, T.; Horino, H.; Koshiro, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504–512.
4. Tsuji, H.; Yagi, F.; Hattori, H.; Kita, H. *J. Catal.* **1994**, *148*, 759–770.
5. Stapp, P. R. *J. Org. Chem.* **1973**, *38*, 1433–1434.
6. Bunce, R. A.; Shellhammer, Jr., A. *J. Org. Prep. Proc. Int.* **1987**, *19*, 161–166.
7. Pasha, M. A.; Ravindranath, B. *Ind. J. Chem.* **1985**, *24B*, 1068–1069.
8. Morita, K.-I.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748–3752.
9. (a) Berberich, H.; Roesky, P. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1569–1571; (b) Onozawa, S.-Y.; Sakakura, T.; Tanaka, M.; Shiro, M. *Tetrahedron* **1996**, *52*, 4291–4302; (c) Yokoo, K.; Mine, N.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1985**, *279*, C19–C21.
10. Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 7695–7698.
11. Späth, E.; Lorenz, R.; Freund, E. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 57–68.
12. Fouquet, G.; Merger, F.; Platz, R. *Liebigs Ann. Chem.* **1979**, 1591–1601.
13. Duke, R. B.; Perry, M. A. *Chem. Abstr.* **1970**, *72*, p12127w (US Patent 3468927, 1964).
14. Merger, F.; Platz, R.; Fuchs, W. *Chem. Abstr.* **1971**, *75*, p76165b (Ger. Offen. 1957301).
15. Meth-Cohn, O. J. *J. Chem. Soc., Chem. Commun.* **1986**, 695.
16. Li-monoalcoholates were typically prepared in dry THF or hexanes under argon in concentrations of 0.1–0.5 M by the following methods: (a) *n*-BuLi (100 mol%) was added at 0°C into the dissolved diol and stirred for 60 minutes before use. (b) LiH was first washed carefully with dry hexanes under argon in order to remove oil from the suspension. Some solvent was added into the clean LiH followed by addition of 1,3-dioxan-4-ol in THF (or hexanes) slowly at 0°C.
17. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
18. The reaction was quenched with 400 mol% of H_2O (compared to amount of $LiAlH_4$) and the precipitate formed was filtered off. If a larger amount of H_2O was used, a gel like product is easily formed and the yield will be reduced. The precipitate was washed with THF, the solution dried over Na_2SO_4, filtered and evaporated yielding diol **9** with high purity (>99.5%).
19. The rather low yield of **9** was due to drying under reduced pressure (0.1 mmHg) during which some diol was evaporated. In test reactions monomeric HPA **8** was reduced with $LiAlH_4$ to **13** with 90% isolated yield.