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The Tishchenko reaction and its modifications in organic synthesis

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ABSTRACT

Tishchenko esterification is an efficient method for the production of esters from the corresponding aldehydes, and it has been utilized for several different purposes during the last century. In the 1990's it has been 'rediscovered' due to its new, selective, and easy applications in asymmetric synthesis including modifications in the creation of β-hydroxy monoesters from β-hydroxy ketones with aldehydes giving excellent stereoselectivities and high yields. These features can be utilized in synthetic organic chemistry among the large number of different natural products bearing such a functionality and have already been used in many applications.

1. INTRODUCTION

In 1906 a Russian chemist, W. E. Tischtschenko, reported the conversion of aldehydes to dimeric monofunctional esters in the presence of aluminium alcoholates and magnesium alcoholate catalysts (step **1**→**2** in scheme 1) [1]. In this reaction a hydride shift takes place from one aldehyde to another and it can be considered as a redox reaction [2]. This finding offered many advantages compared to the similar

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results reported earlier by Claisen with sodium alcoholates and benzaldehyde [3]. With aluminium alkoxides the Tishchenko esterification can proceed smoothly with both enolizable and nonenolizable aliphatic and aromatic aldehydes in moderate to good yields whereas with sodium alcoholates only aromatic aldehydes can be converted to the esters. Since those days this reaction has been utilized in several different applications especially in industrial processes in the preparation of ester moieties [4]. Solutions are now more complicated and variable. During the last decades understanding of stereochemistry has grown and spread explosively. The Tishchenko reaction was one of those old synthetic methods which were rediscovered because of its excellent new applications giving clean and fast reactions with excellent stereoselectivities. Several different modifications of the Tishchenko reaction have emerged, and in order to clarify their features and point out the main limitations and differences in each case, the following divisions were made:

a) **The traditional Tishchenko reaction.** The simple Tishchenko reaction between two similar aldehydes **1** gives a simple (dimeric), monofunctional ester **2** in the presence of a Lewis acidic catalyst.

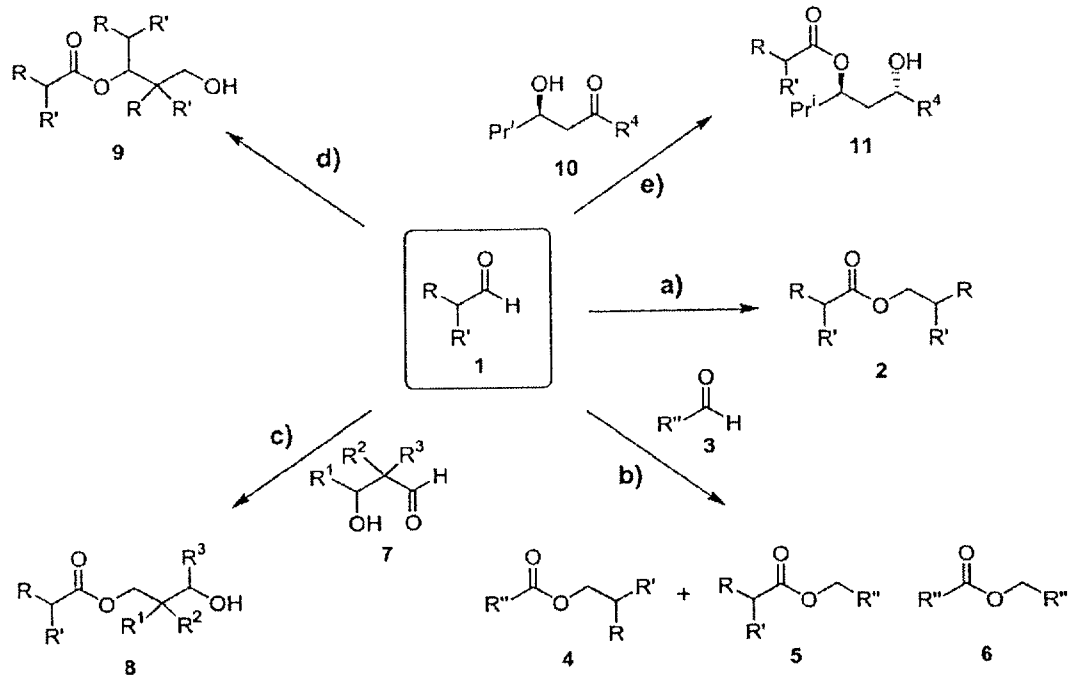
b-c) **Mixed Tishchenko reaction.** In the mixed (crossed) Tishchenko reaction, two different aldehydes **1** and **3** are converted to one or a mixture of different esters **4, 5** and **6**. Another solution of the mixed Tishchenko reaction is the formation of a 1,3-dioxan-4-ol type acetal between β-hydroxy aldehyde **7** and some other aldehyde **1**. The acetal formed is converted to a monoester **8** of the 1,3-diol with a base catalyst. This method can be considered as a modification of the mixed Tishchenko reaction but we will discuss it separately because the mechanism and the product is similar to the aldol-Tishchenko reaction.

d) **The Aldol-Tishchenko reaction.** This modification has been divided to two separate modifications, homo and hetero aldol-Tishchenko reactions. In the former is used and it reacts first with aldol reaction to produce a β-hydroxy aldehyde which forms a hemiacetal with third molecule of **1**. modification only one enolizable aldehyde **1** This hemiacetal will then be converted to monoester of 1,3-diol **9** in the presence of suitable base catalyst. In the latter modification aldehyde **1** reacts with the aldol reaction with different aldehydes, ketones or enolates and is followed immediately by a Tishchenko reaction giving the 1,3-diol monoester usually with excellent *anti*-stereoselectivity.

e) **The Evans-Tishchenko reaction.** This is the last modification discussed in this paper, but still an extremely useful modification in organic synthesis presently. Enantiopure β-hydroxy ketone **10** reacts to ester **11** in the presence of a transition metal catalyst with an excellent *anti*-selectivity which is usually difficult to obtain with high stereoselectivities. This can be considered as a special case of the aldol-Tishchenko reaction due to similar mechanism and the products.

These modifications have been presented in scheme 1 and the main features are discussed below. However, a common feature for all these modifications is a hydride shift between two aldehydes (or an aldehyde and a ketone) giving an ester usually in good or excellent yield [5]. In some cases acetal formation between the aldehyde and β-hydroxy aldehyde is the initial step leading to an intramolecular hydride shift. All the modifications described above are discussed in detail in the following text giving basic information highlighted with the latest work using the modifications as tools in modern organic synthesis.

The high intrinsic reactivity of aldehydes must be taken into account in choosing the



Scheme 1. Modifications of the Tishchenko reaction

reaction conditions in order to avoid undesired side reactions. The most common side reactions observed under Tishchenko reaction conditions are the aldol- [6], Tollen's- [7], The Cannizzaro reaction [8], oxidation by atmospheric air, transesterification [9], hydrolysis of the products [10] and the Meerwein Ponndorf-Verley (later MPV) reduction [11] /Opp-ennauer oxidation [12]. In some cases under certain conditions even different modifications of the Tishchenko reaction can be competitive with cach other. However, the balance between the Tishchenko reaction and side reactions can be controlled by proper choice of the catalyst, reaction temperature and the solvents.

The name of this reaction has caused some confusion. During the 20th century it has been reported with a number of different forms. Name Tishchenko reaction is the most used one even if it differs from the name of the founder. (It has also been called a Tischtschenko reaction, after its discoverer, and also a Tischenko reaction.)

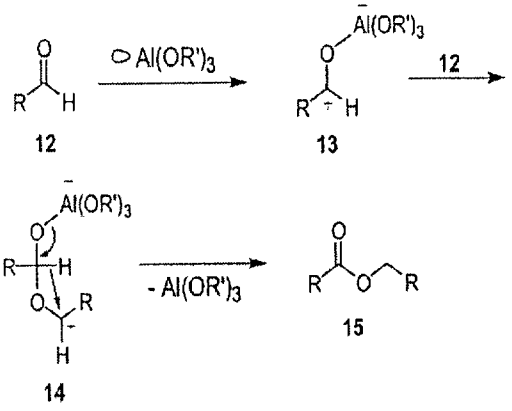
2. TRADITIONAL TISHCHENKO REACTION

In 1887 Claisen found that treat-ment of benzaldehyde with a simple sodium alcoholate gives benzyl benzoate in good yield [3]. Later, the Russian chemist W. E. Tischschenko reported that aluminium alco-holates catalyze the same reaction, not only for benzaldehyde but also for enolizable aldehydes bearing an α-proton, giving simple, monofunctional esters as the product (**1→2** in Scheme 1) without any aldol products [1]. Since then Tishchenko esterification has been closely related to aluminium alcoholates but later successful use of a wide selection of different metal catalysts have been studied and reported. The requirement for the catalyst is sufficient Lewis acidity. This reaction is used in industry in the preparation of a wide range of monoesters been used e.g. as solvents, paint ingredients, lubricants. For instance, eth-yl acetate has been produced with thes method [13].

2.1. MECHANISTIC ASPECTS

2.1.1. TRADITIONAL ALUMINIUM ALKOXIDE CATALYZED

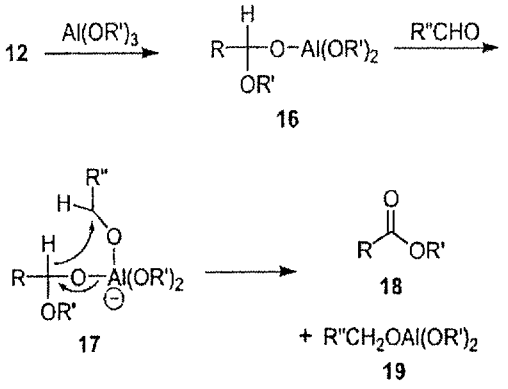
The mechanism of the Tishchenko reaction to the dimeric ester with $Al(OR)_3$ catalysts has been investigated and three different mechanistic proposals have been suggested which all have some common features but also differ considerably from each other. The first and the most commonly used one was presented by Lin *et al.* in 1952. According to this mechanism, the esterification proceeds in three separate steps (Scheme 2) [14]. An empty



Scheme 2. Mechanism Awith $Al(OR)_3$ catalysts

porbital of the aluminium first reacts with the carbonyl oxygen of the free aldehyde **12** to generate alkoxide **13** which is then attacked by a second molecule of **12** giving alkoxide **14**. After hydride shift the catalyst is liberated and monoester is **15** formed.

Ogata *et al.* have studied the use of different aluminium alkoxides in the Tishchenko reaction of benzaldehyde in more detail [15]. They reached the same conclusion as *Lin et al.* in mechanism A (Scheme 2), that the aldehyde is first attached to the aluminium catalyst. The difference in mechanism B (Scheme 3) presented by Ogata et al. was an alkoxide-



Scheme 3. Mechanism B with $Al(OR)_3$ catalysts

transfer from catalyst to the product ester (instead of a direct hydride shift) giving a new alcoholate **16**. This initial alkoxide transfer was unambiguously proven to take place when a mixed ester **18** was obtained in the product mixture. Esterification of acetaldehyde with a high concentration of $Al(O^iPr)_3$ showed also that initial rate of the formation of isopropyl acetate was faster than that of ethyl acetate. After alkoxide transfer another aldehyde R" CHO coordinates to **16** followed by an intramolecular hydride shift giving rise to the crossed ester **17** and the catalyst **18**. Similar propagation continues activated by the catalyst **18**. The use of several $Al(OR)_3$ catalysts was studied and alkoxide transfer was found to be both sterically dependent and aldehyde dependent [16]. In experiments with tertiary alkoxides the occurrence of MPV reduction can be avoided. If bulky alkoxides (R' = *t*-Bu) were used in the catalyst this first coordination of aldehyde to aluminium (**12**→**16** in Scheme 3) was found to be the rate-determining step. In the case of less bulkier alkoxides this initial coordination was extremely fast and hydride shift (**17**→**18** in Scheme 3) was found to be the rate-determining step. The amount of mixed ester 18 was usually related to the amount of the catalyst. If the catalysts bore primary or secondary alkoxide groups, the formation of

MPV reduction products, aldehyde or ketone respectively, was observed in the product mixture.

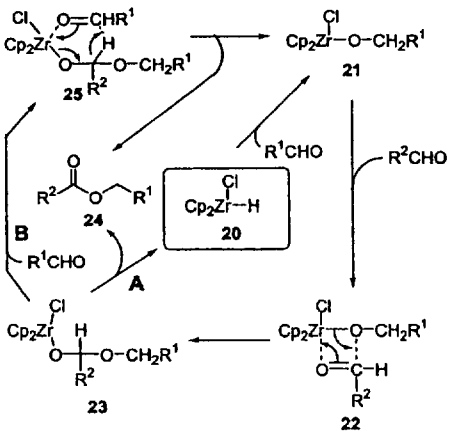
Ogata *et al.* and others studied this alkoxide in more detail and concluded that mechanism B takes place.

Maslinska-Solich *et al.* have studied the mechanism by means of asymmetric induction [17]. They used chiral 2-phenyl propanal as the substrate and different alkoxides with chiral alkoxides such as $Al(menthol)_3$ and $Al(2\text{-}bornanyl)_3$. In their studies, e.g. with a Al-menthol catalyst, they observed the formation of a catalytic amount of menthone which is a indication of MPV-reaction being the initial step. They found that this formation of new mixed alkoxide occurs via transition states following Cram's rule. The rest of the mechanism proceeds as proposed by Ogata *et al.* (Scheme 3). Furthermore, the presence of a small amount of a mixed ester was observed where the alkoxide group of the initial catalyst was the acid part of the ester. This is due to the formation of the free aldehyde from the alcohol of the aluminum alkoxide, most likely via the MPV-mechanism.

The possibility of a radical mechanism has been presented when metallic alkali metal is the catalyst in the Tishchenko esterification of aromatic aldehydes [18]. The reaction of benzaldehyde over catalytic lithium or sodium undergoes a Cannizzaro reaction in several solvents like benzene, ether, THF, DME and hexane. Only lithium in hexane gave benzyl benzoate as the main product. In addition, the presence of a catalytic amount of biphenyl was found to promote the reaction. The esterification proceeded with several other aromatic aldehydes in excellent yields. The indications of the radical mechanism were for example a) a deep bluish-green color of the reaction mixture, b) the reaction was inhibited when radical scavengers such as nitrosobenzene were added, and c) the reaction was promoted by electron-transfer agents such as benzoyl peroxide, biphenyl and azobisisobutyro-nitrile.

2.1.2. TRANSITION METAL CATALYZED

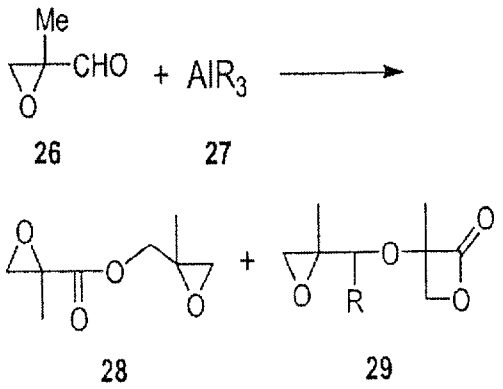
The first mechanistic explanation for Tishchenko esterification with transition metal catalysts was provided by Yamamoto *et al.* in 1978 [19]. They converted both aliphatic and aromatic aldehydes to the ester in the presence of $RuH_2(PPh_3)_4$ catalysts under mild conditions and without appreciable side reactions. The initial step is the coordination of hydridoruthenium complex to the aldehyde and hydride transfer from aldehyde to the metal ($RCHO + M \rightarrow RCOMH$). In the next step the second aldehyde is coordinated to the metal and the hydride is transferred from ruthenium to the carbonyl carbon of the aldehyde. The same group has later analyzed the mechanism of $RuH_2(PPh_3)_4$ catalyzed Tishchenko esterification more thoroughly [20]. The mechanism has been investigated in more detail by several groups. Morita *et al.* have confirmed the same mechanism with zirconocene catalysts (Scheme 4) [21]. There are some



Scheme4. Mechanism catalyzed by zirconocenes

common features with the mechanism B discussed earlier in the case of $Al(OR)_3$ catalysts where the alkoxide of the catalyst will be transferred to the ester under formation. In the transition metal catalysis, it is the hydride (instead of alkoxide group of the aluminum catalyst) which is transformed to the coordi-

nated aldehyde creating an active alkoxide catalyst **21** in the initial step. Alkoxide **21** further reacts with another aldehyde and undergoes similar alkoxide transfer to the aldehyde to give compound **23**. Two alternative pathways (A and B) have been presented for the formation of ester **24**. When an equimolar amount of deuterium labeled zirconocene (hydride replaced with deuterium) was used together with the aldehyde, only the formation of alcoholate, where deuterium has been transferred to the aldehyde carbonyl carbon, was observed. When another equivalent of the aldehyde was added, ester **24** was obtained. Although many transition metal catalysts are very effective in the Tishchenko reaction they are not basic enough to enolize aldehydes and thus do not give aldol products as the side products. Unfortunately, many metal hydrides like Cp_2ZrH_2 are also efficient hydrogenating catalysts and small amounts of alcohol can be obtained as the side product. Morita *et al.* were unable to determine which is the mechanism the reaction follows, pathway A (via a direct hydride shift recreating the initial catalyst **20**) or pathway B(via a six membered transition state **25**) in Scheme 5. According to the previous results of mechanistic studies with aluminum alkoxide catalysts, one could expect pathway B to be more reliable.



Scheme 5.

2.2.THE CATALYSTS ACHIEVING TISCHENKO DIMERIZATION

The first requirement for the catalysts is a sufficient Lewis acidity typical to the traditionally used $Al(OR)_3$ but several other catalysts have also been found to catalyze this particular reaction very effectively: alkali metals, alkali metal alkoxides [22], lithium nitride [23], alkaline earth metal oxides, some Grignard reagents [24], boric acid, alumina supported KF [25], CuO^tBu-PPh_3, Ph_2MnPCy_3 [26], metallocenes, $LiWO_2$, organolanthanoids, lanthanide halides, and lanthanide(amide) complexes.

2.2.1. ALCOHOLATES

The advantages of the aluminium alcoholates is their capability to esterify both aliphatic and aromatic aldehydes to the corresponding monofunctional esters almost quantitatively [27]. These catalysts are Lewis acidic enough to catalyze the Tishchenko reaction and so weak bases that several side reactions like aldol reaction do not occur [28]. However, The MPV reaction can be obtained in catalytic amounts depending on the bulkiness of the alkoxy group in the $Al(OR)_3$ catalysts [29]. Also, the reaction temperature was reported to effect to the Tishchenko reaction. In the presence of aluminium alkoxide catalysts the polymerization of aldehydes takes place at low temperatures (below -40°C) and traces of aldol products can be obtained at higher temperatures (>40°C). The yields of Tishchenko reaction (*n*-butyl *n*-butyrate) increases above -20°C but decreases above +20°C. On the other hand, the MPV reaction occurs as a side reaction and is gradually promoted as the reaction temperature is raised. The presence of carboxylic acids and anhydrides also promotes the aluminium alkoxide catalyzed Tishchenko reaction [30]. The reaction is inhibited in the presence of water and alcohols but in the presence of carboxylic acids the reaction rate is increased due to the formation of highly active dialkoxyaluminium carboxylate catalyst.

Addition of Lewis acids such as aluminium trichloride, zinc halides and mercury chloride has also been shown to enhance the reaction rate. In 1923 Child and Atkins showed that the presence of certain Lewis acidic metal salts promotes the Tishchenko reaction of aldehydes to monofunctional esters when aluminium ethoxide was used as the catalyst [31]. For example, a catalytic amount of $HgCl_2$, $ZnCl_2$ or $CaCl_2$ increased the yield considerably. On the other hand, the presence of simple alcohols decreased the yield.

Tishchenko esterifications of aldehydes bearing a hetero atom or alkenyl substituent are sometimes problematic. For example, dimerization of furfural with common catalysts is usually observed in low yield, if at all. However, for this particular case sodium phenoxide has been reported to be efficient. On the other hand, with aliphatic aldehydes alkali metal alkoxides give mainly the aldol reaction (*vide infra*).

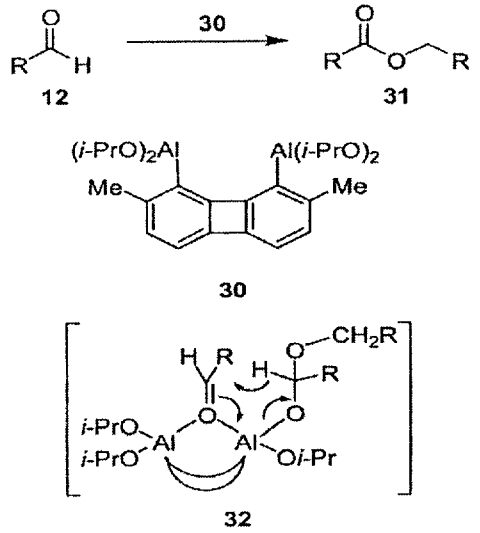
Also, tris(trimethylsiloxy)aluminum has been reported to catalyze the Tishchenko reaction as well as the corresponding aluminum *t*-butoxide. Thus, at higher temperatures the $Al(OSiMe_3)_3$ was reported to be less active [32]. Aluminium haloalcoholates have been reported to give faster reaction compared to the corresponding aluminium alcoholates. This is due to better dissociation of these haloalcoholates to the monomeric form [33].

Jedlinski & Kowalczuk have studied the esterification of 2,3-epoxyaldehydes to the corresponding dimer and found that in addition to the formation of the expected **28**, rearrangement of the epoxy group to β-propiolactone **29** takes place especially when there is an electron donating group (e.g. alkyl in α-position) attached to the aldehyde [34]. This reaction can be carried out with aluminium alkoxides but also with trialkyl aluminium compounds to give lower yields of the rearranged product. The activity of trialkyl aluminium and aluminium alkoxides investigated was the following: (R=)

$OCH_2{}^tPr > OEt > O^tPr > CH_2{}^iPr > {}^nBu > Et.$

However, trialkyl aluminium compounds give faster conversion than aluminium alkoxides, presumably due to higher nucleophility of the alkyl group.

Very recently, during the development of bidentate Lewis acid chemistry, Ooi *et al.* have created a (2,7-dimethyl-1,8-biphenylenedioxy) bis-(diisopropoxyaluminium) catalyst **30** and reported its use in the Tishchenko esterification of aldehydes with excellent yields (Scheme 6) [35]. Catalyst **30** is env-



Scheme 6. Bidentate aluminium alcoholate catalyzed Tishchenko esterification

ironmentally benign and non-toxic compared to many transition metal catalysts. The reaction of several different aldehydes was complete in 0.2-0.25 hours at room temperature giving high isolated yields of ester **31**. In the case of cyclohexyl carboxaldehyde the isolated yield was 98-99%. The amount of the catalyst can be rather low, even 0.2 mol% without any loss of yield. A corresponding reaction with 0.2 mol% of $Al(O^iPr)_3$ under similar reaction conditions gives only a trace of the product ester. The high efficiency of this bidentate catalyst has been explained by double activation of the

aldehyde in the transition state **32** by both aluminium atoms of the catalyst. This assumption is in line with the previous statement (see chapter 2.1. Mechanistic aspects) that with sterically non-hindered aluminium alkoxides the hydride shift is the rate determining step and here the catalyst **30** considerably accelerates this step.

Copper alkoxide complexes have also been investigated and reported to achieve the Tishchenko type dimerization [36]. CuO^{t}Bu alone is totally inactive but after the addition of a suitable ligand the catalyst formed induces the reaction. The catalyst has been studied only in the esterification of benzaldehyde to benzyl benzoate in poor to good yields. The ligands used are phosphines or amines and give the following yields when the reaction proceeds at room temperature in THF over 48 hours: ^{n}Bu$_3$P (83%), Ph$_3$P (68%), ^{t}BuNC (61%), (MeO)$_3$P (49%), C_5H_5N (30%), Et$_3$N (27%), CO (0%). These results (with the corresponding results obtained in the MPV reaction) indicate that electron donating ligands promote the reaction. This is due to the increased nucleophilicity of cuprous alkoxide and the higher reactivity of the carbonyl group of the aldehyde [37].

2.2.2. ALKALI AND ALKALI EARTH METAL BASED CATALYSTS

Simple alkali metals have been reported to catalyze dimerization of aromatic aldehydes to the corresponding esters with good yield. However, the reaction is solvent dependent: Tishchenko product was observed only in hexane (clearly an apolar and aprotic solvent) while in benzene, ether, THF, and DME only Cannizzaro products were observed. The reaction rate can be increased by the presence of biphenyl and other electron-transfer agents (like benzoyl peroxide and azobisisobutyronitrile).

Seebauer *et al.* have studied the correlation between the physical properties of the different alkaline earth metal oxides and the catalytic activity in the Tishchenko reaction [38]. They examined the effect of electronegativity differences, metal-oxygen bond length, oxygen partial charge, and oxygen Madelung potential in the esterification of benzaldehyde. The last two magnitudes were found to correlate with the reactivity quite well and the electronic polarizability of the catalyst was found to give the best correlation. The results showed that the more polarizable the oxygen is (carrying more partial negative charge) the faster esterification was observed:

BaO > SrO > CaO > MgO >> BeO

They also noticed that the hardness/softness of the oxides correlates directly with the reactivity. The softer (more polarized and more basic) the catalyst is, the faster the Tishchenko reaction. Gas phase Tishchenko reaction of formaldehyde to methyl formate has been reported also with several other metal oxides such as Nd_2O_3, SnO, ZnO, PbO, CdO and NiO [39].

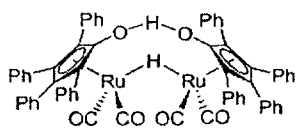
The Cannizzaro-Tishchenko reaction of metal alcoholates ROMgBr and NaOR have been reported to give formate esters with formaldehyde [40]. The alkoxides are easily prepared by means of treatment of the alcohol with the corresponding Grignard reagent or alkali metal hydride. The alcoholate reacts first with one equivalent of formaldehyde to RO-CH_2O-M which forms a six membered ring transition state with another equivalent of formaldehyde which is an acceptor of hydride shifted from the coordinated metal alkoxide. One equivalent of methanol is formed as the side product. However, the reaction is not a typical Tishchenko reaction because a stoichiometric amount of methoxide is formed -as the side product. The reaction can be carried out with all primary, secondary and -tertiary alkoxides.

2.2.3. TRANSITION METAL BASED CATALYSTS

The first transition metal catalyzed Tishchenko esterification was reported by Horino *et al.* in 1978 where both aliphatic and aromatic aldehydes were converted to the

dimeric esters in the presence of ruthenium-(II)-dihydrotetrakis(triphenylphosphine),-$RuH_2(PPh_3)_4$ [21]. They studied a wide variety of different metal catalysts (Fe, Co, Pt, and Pd) with different ligands giving poor yields or no esters at all. Uniquely, $RuH_2(PPh_3)_4$ and many other low valence ruthenium complexes were found to give high conversions and yields. Transition metal catalysts are sensitive towards chelating compounds, and addition of e.g. PPh_3, pyridine or water inhibits the reaction. It was later discovered that diphenylmanganese(II) complexes catalyze this reaction as well. A high purity of the aldehyde is essential for high conversions and high yields. The presence of carboxylic acid and water usually inhibit the reaction drastically, but the ruthenocene catalyst **33** is an exception and the presence of formic acid boosts the reaction rate dramatically.

Shvo *et al.* have reported the best yields of Tishchenko dimerization by using ruthenium complex $[(C_4Ph_4COHOCC_4Ph_4)(\mu\text{-}H)][(CO)_4Ru_2]$ **33** or its isostructural complexes in the presence of a catalytic amount of formic acid (Scheme 7) [41]. They observed this



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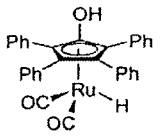

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Scheme 7. (η^4-C_4Ph_4-CO)$Ru(CO)_3$ dimer and monomer

homogeneous bimolecular disproportionation reaction in the presence of an extremely low concentration of catalyst **1** (0.001-0.0002 mol%) and in the presence of 5-10 mol% of formic acid. Furthermore, the reaction can be carried out in the presence or absence of solvent and under mild conditions. It should be mentioned that this method gives excellent conversion, yield and selectivity and is compatible with a variety of aliphatic and aromatic aldehydes. Also the initial turnover frequency of 5000 h^{-1} and the measured overall turnover number of 20 000 is impressive. The authors also observed that increasing the electron density on the ligand and the metal itself accelerates the reaction. Thus, it is the monomeric form **34** of the catalyst which is the reactive one and the role of formic acid is to generate a new hydride for the ruthenium.

Catalysts similar to **33** with osmium as the metal have also been studied in the Tishchenko reaction but they were found to be ineffective [42]. The diminished catalytic activity of the osmium complex is due to stronger Os-CO bonding which makes the complex more stable but less active as the catalyst.

Some ruthenium catalysts have been reported to give combined Rosenmund-Tishchenko reaction with acid chlorides. In a typical Rosenmund reaction an acyl chloride is converted to an aldehyde. However, the presence of a strong organic base is required in order to quench the HCl formed during the reaction, but the base should possess a low nucleophilicity to avoid reaction with the acid chloride. Grushin et al. have reported that Wilkinson's catalyst $[(PPh_3)_3Rh(H)Cl]$ is capable of catalyze both Rosenmund and Tishchenko reactions of aromatic acid chlorides to esters in good (52-85%) overall yields [43].

Metallocenes (Cp_2MH_2) of group IV metals, except titanocene, are also very effective catalysts for Tishchenko reaction. The reaction proceeds in the absence of solvent with 5 mol% of the catalyst and at 0°C in 30 minutes to give esters from 67-95% yield and excellent conversions depending on the used aldehyde and the catalyst [21]. However, the efficiency depends on the substituents of the metallocenes: The stronger the metal-substituent bond is, the lower the catalytic activity. This can be clearly seen in experiments with zirconocene and hafnocene where hafnocene gave slightly better conversion of aldehyde and higher yield of the ester. The reactivity followed the order:

$Cp_2Hf > Cp_2Zr > Cp_2HfH_2 > Cp_2ZrH_2 > Cp_2Hf(H)Cl > Cp_2Zr(H)Cl > Cp_2Ti$

Experiments with the catalysts Cp_2TiH_2, Cp_2HfCl_2, and Cp_2HfCl_2 showed these to be completely inactive. (The plausible catalysts Cp_2Hf, Cp_2Zr, and Cp_2Ti were prepared from the corresponding Cp_2MCl_2 by treatment of 2 equiv of *n*-BuLi. These catalysts have also been used in hydrogenation reactions and with aliphatic, non-branched aldehydes some alcohol can be observed in the reaction mixture especially with Cp_2ZrH_2.) Transition metal catalysts with electron withdrawing ligands such as halides are usually inactive in the Tishchenko reaction.

Certain iridium complexes have also been found to convert simple aldehydes to esters[44]. Especially with *trans*- $ROIr(CO)(PPh_3)_2$ paraformaldehyde is converted to the methyl formate with 90% yield in 2 days at room temperature and acetaldehyde to the ethyl acetate with 75% yield within 5 days (R = Me in the catalyst). The role of the ligands in the catalyst is crucial. For example, the esterification of formaldehyde proceeds with alkoxide substituents where R = Me, ^{i}Pr, ^{t}Bu, ^{n}Pr and the esterification of acetaldehyde with substituent R = Me. The initial step of the reaction is coordination of the aldehyde to the coordinatively unsaturated (16-electron) metal, followed by alkoxide transfer from the catalyst to the aldehyde. The rest of the mechanism occurs in the same manner as shown earlier in Scheme 4 [45]. If the Lewis acidity of the metal is lowered (phenoxide, trifluoroethoxude or halide in place of alkyl alkoxide), the catalyst loses its activity. The 18-electron complex *trans*-$ROIr(CO)(PPh_3)_3$ was found to be inactive.

Disodium tetracarbonylferrate (II) is also an active catalyst in the Tishchenko esterification but it can be utilized only with aromatic aldehydes [46]. The presence of sodium makes the catalyst so basic that aliphatic aldehydes undergo aldol reaction. Benzaldehyde can be converted to the benzyl benzoate in 95% yield in THF at +25°C in 40 hours. The reaction rate depends on the electronic effects of the substituents in the aromatic ring. The highest reactivity was obtained with *p*-ClC_6H_4CHO (an electron withdrawing substituent) but anisaldehyde (an electron releasing substituent) reacted rather sluggishly. It was suggested that the reaction is influenced by the electron density on the carbonyl carbon of the aldehyde which is attacked nucleophilically by the ferrate.

Transition metal alkoxides have also been utilized in the Tishchenko esterification of aromatic aldehydes. Especiallybis(aryloxo) iron(II) and bis(alkoxo)iron(II) such as $Fe(OCH_2C_6H_5)_2(bpy)$ have been reported to convert benzaldehyde to benzyl benzoate in 63% yield [47].

2.2.4. LANTHANIDE BASED CATALYSTS

Lanthanide amides, $M[N(SiMe_2)_3]$ (M = La, Sm, or Y), are a potential group catalysts [48]. The catalyst can be easily prepared and it is stable enough for use in several batches. With these catalysts, especially with lanthanum (M = La), dimeric esters can be obtained in almost quantitative yields. Onozawa et al. have studied the use of pentamethylcyclopentadienyl (Cp*) lanthanoid complexes as the catalysts in Tishchenko reactions of mono and dialdehydes [49]. The catalyst Cp^*_2M CH $(SiMe_3)_2$ is active with a wide range of aromatic and aliphatic α-branched aldehydes. With non-branched and linear aliphatic aldehydes trimeric products were observed due to initial aldol reaction followed by dehydration. However, these catalysts can also induce Tishchenko dimerization of aldehydes which are usually esterified in low yield or not at all, such as furfural and 2-thiophene carboxaldehyde. With aromatic aldehydes the influence of *p* substituents was observed. Electron with drawing substituents increased the yield:

-OMe (3%) < -Me (20%) < -Cl (43%) < -CN (96%)

Organolanthanoid halides (EtLnI ; Ln = Pr, Nd, or Sm) have been reported as Tishchenko catalysts for aldehydes (aromatic and aliphatic with no α-protons) albeit with only moderate yields [50]. In the same paper metallic lanthanoid alone was reported to

catalyze the dimerization with low yields. Thus, the divalent state of the corresponding catalysts of Yb and Eu is more stable (than of Pr, Nd, or Sm) and the latter metal catalysts give the Grignard type products predominantly.

Some lanthanide halides also give Tishchenko esterification of aldehydes with good yields. 0.01 eq. of SmI_2 in THF at room temperature catalyzes a complete conversion of benzaldehyde, butanal, and heptanal to the corresponding esters in 24 hours [51]. Some trimerization of aldehydes in the presence of SmI_2 has also been observed.

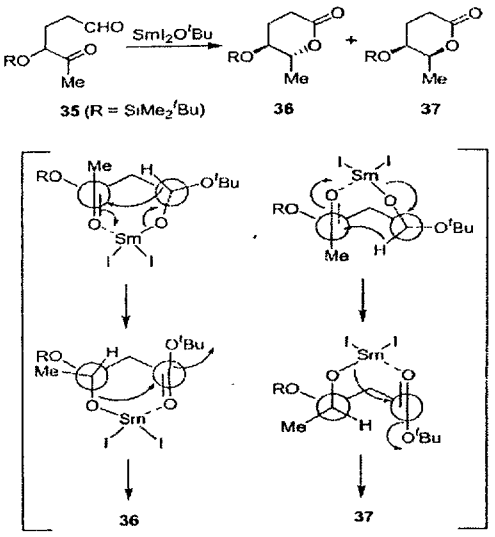
2.2.5. MISCELLANEOUS CATALYSTS

Boric acid has also proved to be an active catalyst, although rather strong conditions are required: at room temperature very low conversion and yield are obtained but raising the temperature increases the yield [52]. The reaction is also very solvent sensitive: Polar solvents quench the Lewis acidity of boron (THF decreases the reactivity considerably and addition of water inhibits the reaction completely). The reaction is usually performed in an autoclave at 250°C and the esters are obtained after 5-7 hours in 50-77% yield depending on the aldehyde. For example, in the case of benzaldehyde, no reaction was obtained at 180°C after 18 h reaction time but at 250°C benzyl benzoate was obtained in 50% yield after 6 hours.

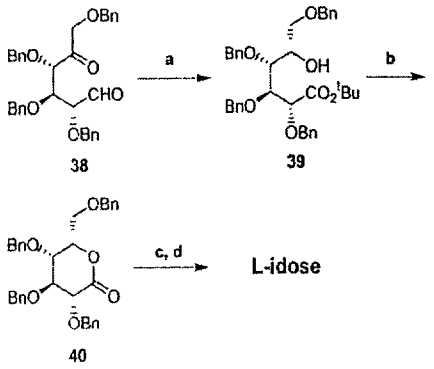
2.3. APPLICATIONS OF THE REACTION

2.3.1. INTRAMOLECULAR CYCLIZATIONS

Uenishi *et al.* have reported the intramolecular Tishchenko cyclization using a trivalent samarium reagent to convert 4-siloxy-1,5-ketoaldehydes **35** into δ-lactones [53]. The use of divalent SmI_2 gave only the pinacol product, while a small amount of MeOH with SmI_2 gave both pinacol and lactone product. The role of methanol was suggested to be *in situ* formation of trivalent SmI_2OMe with SmI_2. Thus, with SmI_2O^tBu only lactone **36** was obtained with *anti*-selectivity exclusively (Scheme 8).



Scheme 8. Tishchenko lactonization

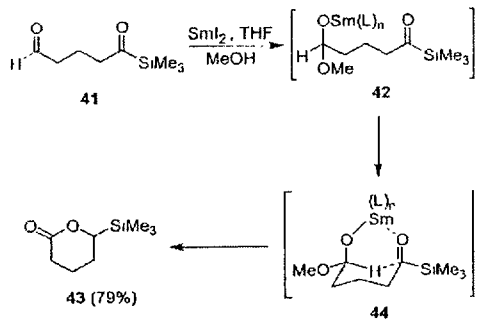


Scheme 9. Intramolecular Tishchenko in the synthesis of L-idose. a) *t*-$BuOSmI_2$, THF. b) 1:1 CF_3CO_2H / CH_2Cl_2, 0°C, 30 min. c) DIBAL (1.1 eq), toluene, -70°C, 1h. d) C-Pd, 1:9 HCOOH:CH_3OH, sonication, 2h.

In the transition state leading to the *syn*-product **37**, steric hindrance between the siloxy group and the ketone group makes the transition state unfavorable.

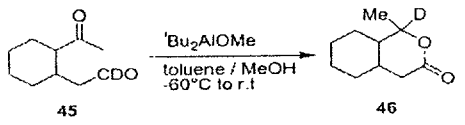
Adinolfi *et al.* have utilized this method successfully in the preparation of unnatuatural L-sugars starting from easily available prote-

cted D-sugars [54]. Ketoaldehyde **38** was easily prepared from such protected Dsugars with Swern oxidation. Under acidic conditions lactone **40** is formed, which is finally reduced and deprotected to give L-idose.
Similar cyclization has been achieved with SmI_2 with a catalytic amount of MeOH in order to initiate the reaction (Scheme 10) [55].



Scheme 10.

The authors believe that MeOH coordinates to the aldehyde carbonyl group in **41** simulatan-eously with the catalyst giving hemiacetal **42** followed by intramolecular hydride shift to lactone **44**. However, it is also possible here that MeOH reacts first with SmI_2 and the rest of the mechanism will proceed via a [6,6]-bicyclic transition state **43**, where intramolecular hydride shift takes place.



Scheme 11.

The mechanism of intramolecular hydride shift and cyclization of δ-keto aldehydes (5-oxo alkanals) has been demonstrated by Lange & Organ by using deuterium labeling to give the labeled lactone **46** [56]. The reaction proves that the Tishchenko reaction is not limited to occurring only between two aldehydes but also between aldehyde and ketone. Thus, it is possible that here also the initial step of the reaction is the alkoxide transfer from the catalyst to the aldehyde group.

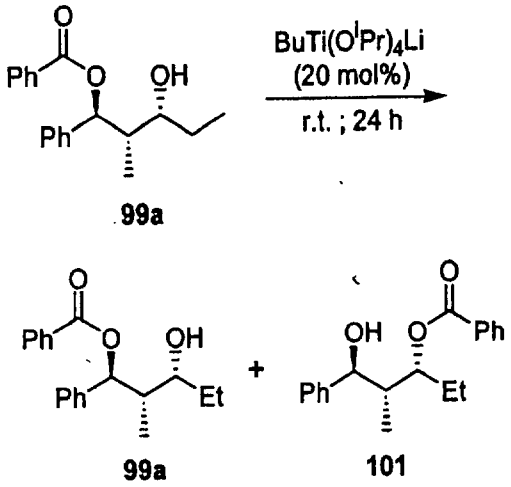
2.3.2. Polymerization reactions

Monofunctional aliphatic aldehydes are known to polymerize at low temperatures in the presence of organo-aluminum compounds to yield crystalline isotactic polyaldehydes [57]. At high temperatures the same aldehydes undergo Tishchenko reaction in the presence of aluminium alkoxides.$AlEt_3$ also catalyses the Tishchenko reaction of e.g. allyloxyacetaldehyde to the simple ester at room temperature but at -45°C and -78°C a white solid polymer can be obtained with high yield [58].

Polymerization by Tishchenko reaction allows several advantages compared with other polymerization techniques. For example in ring-opening polymerization long alkyl chains are difficult to obtain. Also in dicarboxylic acid-diol polymerizations the ratio of substrates needs to be adjusted but in the Tishchenko system there is only one substrate present. Additionally, here the aldehyde groups can remain at the ends of the polymer chain offering the advantage of using the polymer formed as a starting material in e.g. copolymerizations. Tishchenko polymerizations are commonly carried out for aromatic and sometimes for aliphatic diald-ehydes. Several catalysts have been utilized, such $RuH_2(PPh_3)_4$ and SmI_2 to polymerize aromatic aldehydes (terephthal and isotere-phthal aldehydes) and aliphatic aldehydes (1,12-dodecanedial) with 49-95% yield in THF and at 0°C [59]. Polymerization of these aldehydes with SmI_2 gives polyesters with terminal aldehyde groups at both polymer ends. In the presence of benzaldehyde in the reaction mixture an end-capping of the terminal aldehyde functionalities can obtained by formation of an ester functionality ($-CO_2CH_2Ph$). This can be advantageous if the terminal aldehyde groups undergo unfavorable side reactions [60]. In some polymerization processes the polymer with bridgehead aldehydes is unstable and

tends to depolymerize spontaneously even at room temperature but this can be avoided with end capping.

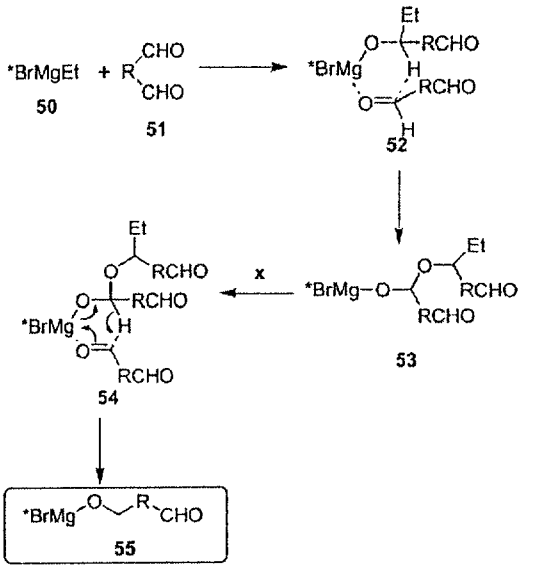
Treatment of glycidaldehyde with a Lewis acidic catalyst, e.g. aluminum isopropoxide, gives a ring-opening polymerization with the Tishchenko reaction [61]. The reaction is known to be temperature dependent. At room temperature glycidaldehyde **47** reacts to polyether **48** but at -78°C the Tishchenko esterification to polyacetal **49** takes place giving a polymer having an unreacted epoxy group as the side chain (Scheme 12). The mechanism is closely related



Scheme 12

to the typical one for aluminium alcoholates as presented earlier in Scheme 3. Here the initial step is the formation of a simple ester between two glycidaldehydes with Tishchenko esterification. Thus the polymerization itself initiates with alkoxide transfer from the catalyst to the β-position of the acid part of the formed glycidaldehyde ester and the opened oxirane group acts as a nucleophile in the polymerization.

Terephthaldehyde and isophthalaldehyde have been reported to polymerize to the corresponding polyester also in the presence of ethylmagnesium bromide-(-)-Sparteine complex **50** and aluminum alkoxides (Scheme 13) [62]. Here the alkyl group of the Grignard

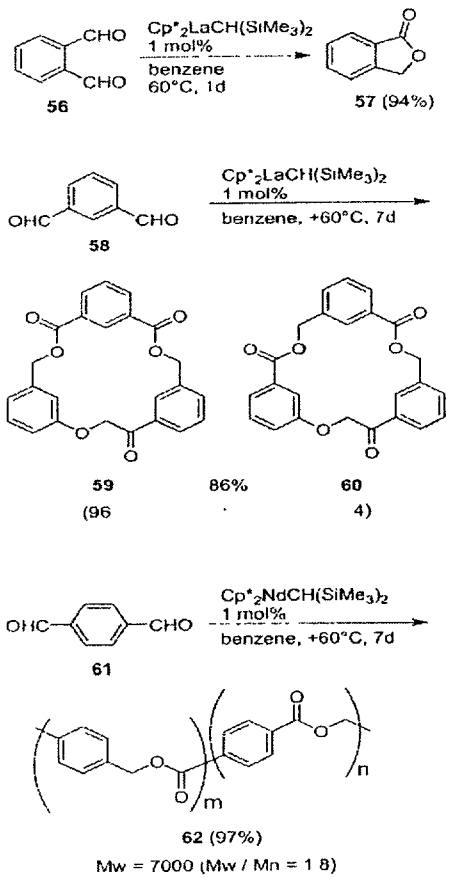


Scheme 13.

reagent is initially transferred to the carbonyl carbon of the aldehyde in a normal fashion and the carbonyl oxygen is coordinated to the magnesium to give alkoxide **52**. Another aldehyde then coordinates to the metal with alkoxide transfer to give compound **53**. After a MPV-type hydride shift an alcoholate **55** is formed. This alkoxide **55** initiates the Tishchenko reaction of the dialdehydes where they are converted to an ester. The diester is formed with an aldehyde functionality at both ends and reacts further by the Tishchenko to the polymer.

The same (-)-Sparteine-ethylmagnesium bromide catalyst has been reported to catalyze asymmetric polymerization of 3 phenylpropanal to a polyacetal having a stabilizing ester functionality at the end of the polymer chain. With this catalyst the polymer with a predominantly one handed helical, optically active conformation is formed, having clearly negative rotation ($[\alpha]^{25}_{365}$ -33° to -56°) [63]. As mentioned earlier in Scheme 12 the low reaction temperature is required here to obtain a polyacetal related to **48**.

The work with lanthanide amides by Onozawa *et al.* has already been discussed. Their work with difunctional *o*- **56**, *iso*- **58** and terephthalaldehyde **61** turned out to give different reactions in the presence of lanthanide based catalysts (Scheme 14) [49]. Treatment of *ortho*-phthalaldehyde **56** with a lanthanide amide gives intramolecular Tishchenko esterification in 94% yield but polymerization can not be observed. In the case



Scheme 14. Lanthanoid amide catalysts with dialdehydes

of *iso* phthalaldehyde **58** the polymerization takes place first giving a polymer related to **62** but this is slowly (in 7 days) converted to more stable trimeric oligomers **59** and **60** by lanthanide catalyzed transesterification. In the reaction of terephthal aldehyde **61** neither intramolecular Tishchenko reaction nor formation of oligomers was observed. Thus, polymer **62** crystallized out from the reaction with almost quantitative yield. The molecular weight was rather low because of the low solubility of the polymer formed in benzene. Onozawa *et al.* have also studied the mechanism of the Tishchenko reaction and concluded the same catalytic cycle as did Ishii *et al.* (Scheme 4). The formation of the active catalyst from the lanthanide complex was explained more exactly here.

3. MIXED TISHCHENKO REACTION

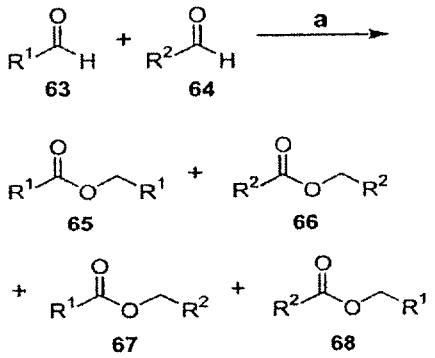
The mixed Tishchenko reaction is also called a crossed Tishchenko reaction. The presence of two or more different aldehydes makes the situation much more complicated compared to the traditional Tishchenko reaction. In the worst case, the product mixture contains all possible combinations between the aldehydes. Two factors can effect the product distribution. First, the aldehyde reactivities are mainly due to electronid effect, although steric factors can play a role. The second major factor is the effect of the catalyst.

3.1. TWO MONO FUNCTIONAL ALDEHYDES

Lin *et al.* [14] and Ogata *et al.* [15,16] have showed that the electronic effects of the substituents in aldehydes play the most significant role here. They examined the use of substituted benzaldehydes with $Al(O^tBu)_3$ and concluded that aldehydes with electron-releasing substituents in the aromatic ring tend to become the acid part of the resulting ester while aldehydes with electron-withdrawing substituents tend to become the alcohol part. They also showed that alkoxide transfer from the catalyst is favored to the aldehyde having the more electrophilic carbonyl carbon (benzaldehyde) rather than an electron rich carbonyl carbon (anisaldehyde).

The mixed Tishchenko esterification has been studied also with several other catalysts

and transition metal catalysts have been used successfully. Specifically, some zirconocenes catalyze the dimerization well. Morita *et al.* have reported Cp_2ZrH_2 and $Cp_2Zr(H)Cl$ aldehydes to give all the possible homo (**65** & **66**) and crossed dimers (**67** & **68**) when *n*-butanal (R = ^{n}Pr) and another aliphatic aldehyde (linear or α-branched) were used in equimolar amounts [21].



Scheme 15. Crossed Tishchenko reaction with zirconocenes. Reactants and conditions: a) **63** (2.5 mmol), **64** (2.5 mmol), $Cp_2Zr(H)Cl$ or Cp_2ZrH_2 (0.25 mmol; 5 mol%), +20°C, 30 min., under argon.

A considerable amount of the corresponding alcohols was formed as well due to hydrogenation of the aldehyde by the catalyst, especially with Cp_2ZrH_2. When benzaldehyde **64** (R^2 = Ph) was dimerized with **63** (R^1 = ^{n}Pr) mainly benzyl butyrate **67** (R^1 = ^{n}Pr, R^2 = Ph) was formed with a good 54% yield. Additionally homoesters **65** and **66** were obtained with 22% yield in a ratio of 99 to 1; respectively. Thus, only a trace of formation of butyl benzoate **68** was observed. This was explained by the better ability of the benzaldehyde to coordinate to the catalyst in the initial step (see mechanism in Scheme 4). The observation deviates from corresponding results obtained in the presence of a $RuH_2(PPh_3)_4$ catalyst wherein homo-dimer **65** was the main product in addition to **67** and **68**. The aldehydes ability to coordinate to the metal is affected by the differences in the steric hindrance between the aldehyde and the ligands of the catalysts as well as the electronic effects.

3.2. 'MIXED ALDOL-TISHCHENKO' RE - ACTION (via 1,3-dioxan-4-ols)

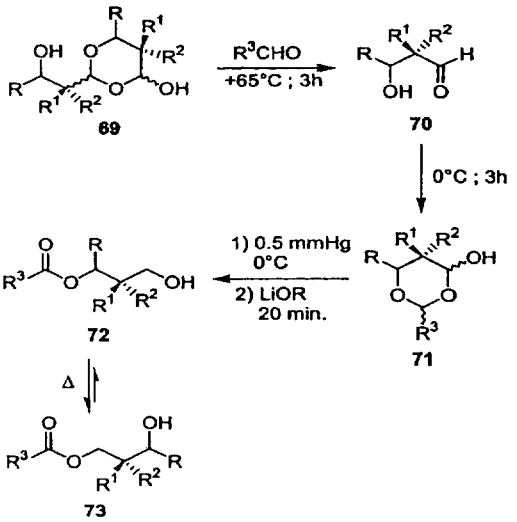
In a mixed aldol-Tishchenko reaction two different aldehydes react with each other. One aldehyde is typically a β-hydroxy aldehyde (aldol product) and the other one is a monofunctional aldehyde. The reaction mechanism of the Tishchenko step is similar to that reported with the aldol-Tishchenko reaction. Thus, the prefix 'aldol' can be confusing because an aldol reaction is not actually involved here. However, this aldol product has been separately prepared and purified before use. The products are also similar to the aldol-Tishchenko reaction but this method allows for a wide modification of the products. In the normal aldol-Tishchenko reaction the product distribution is easy to control if only one aldehyde is used, but here the situation is much more complicated. The challenge is the formation of the desired crossed ester selectively so that the aldol product forms the ester with the third aldehyde. If both aldol reaction and formation of the crossed ester is attempted simultaneously in a one pot reaction, a large number of different products can be observed usually with a low yield of desired product. In our own work we have worked out and outlined some limitations in this particular case. One of our aims was to find out a way to prepare selectively monoesters of 1,3-diols without any side reactions so that the methodology can also be used on larger scales. In this procedure the readily prepared β-hydroxyaldehyde forms a dihemiacetal like cyclic 1,3-dioxan-4-ol with another aldehyde. This dioxanol can be esterified to the corresponding monoester in the presence of certain alkali metal or alkali earth metal catalysts. The reaction has also been reported to undergo even without the catalyst at higher

temperatures [64]. There is an alternative method for the preparation of similar monoesters of 1,3-diols but quite vigorous reaction conditions are required, like high pressure and temperatures [65].

It is known that many aldol products tend to dimerize to a more stable hemiacetal type 1,3-dioxan-4-ol structure **69** which can be easily separated with column chromatography [66]. In our procedure we had to monomerize this aldol product first in order to form the new crossed dimer **71**. Späth et al. have studied the formation of the 1,3-dioxan-4-ol **71** type hemiacetal between the aldol product and another aldehyde. In their experiments they succeeded in preparing a few compounds related to structure **71** [67]. However, the formation of this 1,3-dioxan-4-ol took three days and the product was not esterified further. We studied the conditions affecting the stability of the aldol dimer (dimer of 3-hydroxy pivalaldehyde, later HPA) by means of ^{1}H-NMR in several solvents and temperatures. Polar solvents tend to monomerize the dimer at lower temperatures (95% in monomeric form in D_2O at +25°C) whereas higher temperatures were required in apolar solvents (in CH_3Cl 9% was in monomeric form at +35°C but fully monomerized at +50°C).

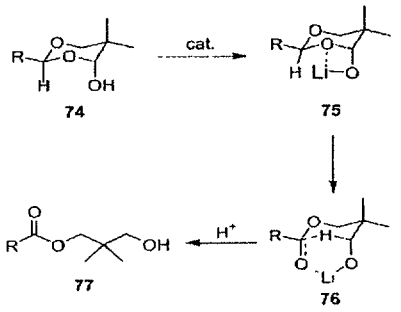
Several different techniques were tried in order to reach fast monomerization of dimeric HPA and formation of the new mixed dimer. Eventually we managed to monomerize the dimeric aldol **69** to monomer **70** at +65°C in excess of another aldehyde. If the other aldehyde is solid, some apolar solvent can be used. The monomerization time should be at least three hours to reach completion and then followed with cooling. If the mixture was cooled to room temperature an equilibrium between the new mixed trimer **62** and monomeric HPA **70** was reached in 2½-3 days and still a significant amount of monomeric HPA was present. It was noticed that the temperature plays a major role here. The new mixed dimer was formed in less than 3 hours when the mixture was cooled to 0°C and not even a trace of monomeric HPA 70 was observed (^{1}H-NMR). The product mixture usually contained 82-91% of mixed dimer **71** (depends on aldehyde excess used) and 9-18% of HPA dimer **69**. An ideal amount of aldehyde (R^3CHO) excess was 5 mol equivalents compared to **70**. A smaller amount reduced the formation of mixed dimer but larger amount gave no significant improvement. However, 1,3-dioxan-4-ols were very unstable and were analyzed with ^{1}H-NMR directly from the product mixture. They could not be isolated without protection of the hydroxyl group (usually acetylation). No hemiacetal in the open form was observed in NMR-studies.

We studied some structures related to the dimeric aldol products by means of molecular modeling (Macro Model 4.5; Monte-Carlo method; MM2 force field) and found that a hydroxyl group of the side chain in ring position 2 (substituent R^3 of compound **71** in Scheme 16) can form a hydrogen bond to the ring oxygens. This side chain also forms a chair like conformation. This could explain the stability if aldol dimers are compared to compounds which are lacking the side chain hydroxyl group. The optimized system is presented in the following scheme (Scheme 16). After the formation of mixed dimer **71** the

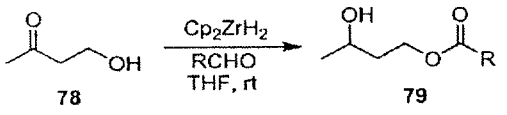


Scheme 16. Mixed aldol-Tischenko reaction

excess of the other aldehyde was removed before the addition of catalyst and Tishchenko esterification in order to avoid aldol reaction (and aldol-Tishchenko) of this free aldehyde. In cases where the excess aldehyde is high-boiling, a catalyst must be used which does not promote the aldol reaction but does promote the Tishchenko reaction, e.g. $Ba(OH)_2$ with ethyl hexanal. The only catalysts reported in the esterification of 1,3-dioxanols are alkali metal and alkali earth metal hydroxides and the corresponding alcoholates of monofunctional alcohols. We believe that it is not the basicity or Lewis acidity which initiates the hydride shift but the metal's ability to coordinate to the dioxanol. In the reaction the hydroxyl group of the ring is first deprotonated and the coordinated metal atom achieves the hydride shift (Scheme 17). We assume that 1,3-dioxan-4-ol **74** will coordinate to the catalyst



Scheme 17. Mechanism of Tishchenko esterification of 1,3-dioxan-4-ols



Scheme 18.

and form a chair like [6+6] transition state **75** which will be presented later in the chapter on the Evans-Tishchenko reaction. Here the coordinated metal pulls electron density and hydride shifts to the carbon connected to both oxygens attached to the metal catalyst more easily [68]. Requirements for the catalysts are basicity (activation of aldol) and sufficient ability to coordinate to the oxygens. Usually it is the Lewis acidity of the catalyst that governs the efficiency of the Tishchenko reaction but here e.g. Lewis acidic aluminum isopropoxide was found to be ineffective which is due to low basicity.

Similar results have been observed lately by Ishii *et al.* in zirconocene catalyzed esterification of β-hydroxy ketone **78** with a free aldehyde [69].

This zirconocene catalyzed esterification gives pure products with good stereoselectivity. Additionally, no intramolecular acyl migration of ester **79** was observed with zirconocene as has been reported for similar products catalyzed by $BuTi(O^iPr)_4Li$ in aldol-Tishchenko reactions.

The same reaction has also been carried out by Scott *et al.* with $Sc(OTf)_3$ catalyst [70]. The reaction temperature was found to be crucial for obtaining good yields and diastereoselectivities. When a mixture of 4-hydroxybutan-2-one **78** and isobutyraldehyde was treated with 10% of $Sc(OTf)_3$ in THF at room temperature, the Tishchenko product **79** was also be obtained but the acetal of isobutyraldehyde with two β-hydroxyketones was the main product. If ketone **78** was added over 2.5 hours to the mixture of isobutyraldehyde and $Sc(OTf)_3$ at -10°C the ester **79** could be obtained with >95% yield. When secondary alcohols were used as the starting material instead of **78**, such acetal formation could not be obtained. In their experiments with related 4-alkyl substituted ketones it was noticed that at higher temperatures lower diastereoselectivities were obtained. This system is also limited to aliphatic aldehydes. With aldehydes lacking acidic α-hydrogens like benzaldehyde and crotonaldehyde the reaction is unsuccessful.

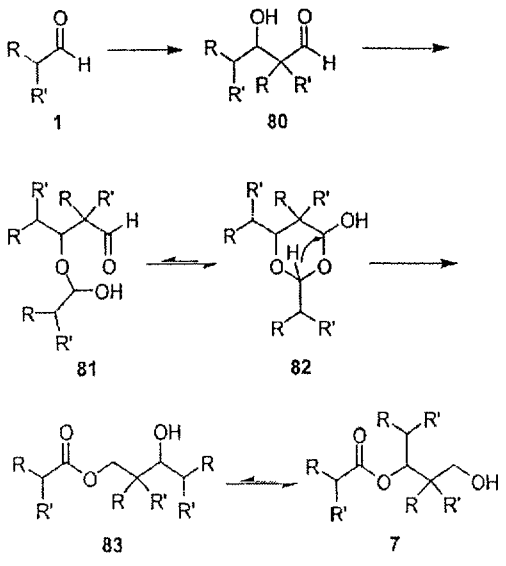
4. ALDOL-TISHCHENKO REACTION

This modification has also been called the Claisen-Tishchenko reaction. The reason for this is due to experiments performed by

Claisen in 1887 with sodium alkoxides and benzaldehyde (see chapter Traditional Tishchenko, above). Thus, when enolizable aldehydes are treated with basic sodium alcoholates, the aldol reaction occurs followed with Tischenko esterification giving monoesters of 1,3-diols as the products. The aldol-Tishchenko reaction can be divided in two main groups: homo and hetero aldol-Tishchenko reactions. In the former one, only one enolizable aldehyde is used and is converted to 1,3-glycol monoesters. In the latter one, usually a ketone (or its enolate), but also aldehydes react with another aldehyde by aldol reaction and then further with an intramolecular Tishchenko esterification. The catalysts used usually bear a basic moiety in order to achieve both reactions. Several other catalysts have been found to catalyze this reaction and in several studies the enolate is first prepared followed with aldol and Tishchenko reactions to the monoesters. Among the latest papers on some aldol-Tishchenko modifications, excellent *anti*-selectivity in the product monoester can be obtained. The hetero aldol-Tishchenko reaction especially is very closely related to the Evans-Tishchenko reaction (*vide infra*). Both reactions could be considered under the aldol-Tishchenko title. They proceed with the same mechanism and the reaction conditions are quite similar. The only differences are the catalyst used which is limited to SmI_2, and the starting material is the readily prepared β-hydroxy ketone in the case of Evans's method. Therefore the aldol-Tishchenko reaction is usually much more difficult to control and gives several possibilities for modifying the final product.

4.1. HOMO ALDOL-TISHCHENKO REACTION

This modification has already been under intensive research for one century due to its considerable industrial importance [71]. The main products of this trimerization of aldehydes are isomers of 1,3-glycol esters which are widely used especially as paint coalescent agents in the coatings industry and as lubricants. They are actually the most used coalescent agents and consumption of e.g. 2-methylpropanal to condensation and esterification products was 260 million pounds in 1997 exclusively in the US market [72]. The steps of the homo aldol-Tishchenko reaction are presented in Scheme 19. The enolizable aldehyde **1** is treated first with a basic catalyst affording the aldol product, β-hydroxy aldehyde **80**, followed by formation of hemiacetal **81** with the third molecule of the same aldehyde and finally to 1,3-dioxan-4-ol **82** type structure [73]. The hemiacetal is converted via intramolecular hydride shift to 1,3-diol monoesters **83** and **7** as the main products. In the aldol-Tishchenko reaction the aldol reaction takes place first and is followed by Tishchenko reaction, whereas in the Evans-Tishchenko readily available β-hydroxyketone (aldol product) is used as the starting material. The mechanism was presented for the first time by Merger *et al.* in 1979 (Scheme 19) [74].
Hemiacetal **81** can form an intram-olecular hemiacetal to give substituted 1,3-dioxan-4-ol derivatives **82** (also called aldoxan) [75]. Glycol monoesters **7** and **83** can be obtained



Scheme 19. Homo aldol-Tischenko reaction (only one enolizable aldehyde)

with good yields because significant side reactions do not usually occur. It is possible that with some aliphatic aldehydes, especially with non-branched ones, a condensation reaction can occur and α,β-unsaturated aldehydes are observed as the main product.

Formation of aldoxan **82** takes place and can be observed if the reaction proceeds at low temperature. However, in mechanistic studies the direct esterification from hemiacetal **81** has been reported to take place [76]. The effects of the chiral catalysts have also been investigated but a clear effect has not been observed due to intramolecular ester interchange caused by the catalyst [77].

The catalysts traditionally used are alkali earth metals or alkali metal hydroxides which are cheap and easy to use on industrial scales [78]. Unfortunately they require the presence of water and give fast and irreversible hydrolysis of the product esters. In addition, alcoholates of monofunctional alcohols have been used in these reactions giving fast reactions and good yields [79]. With these alcoholate catalysts some ester interchange product is formed between the catalyst and the product esters. We solved this problem by using monoalcoholates of 1,3-diols as the catalysts in order to avoid hydrolysis and extra costs arising from the disposal cost of waste water. Furthermore, ester interchange with the catalyst and the product gives the same product if a suitable diol is used in the catalyst. Additionally, these catalysts gave fast and clean reactions [80]. Thus, formation of the diester occurs as a side reaction which is due to metal exchange between the catalyst and the product followed by transesterification. Formation of diester can be minimized if the reaction time is short enough and a weakly coordinating counter ion (potassium) is used in the alcoholate catalyst. In high concentration of the catalyst and with short aliphatic aldehydes the formation of diester has been reported to be higher when the reaction is catalyzed by $LiWO_2$ [81]. We have observed the best results when 2-methylpropanal was treated with sodium 2,2-dimethyl-3-hydroxyl-1-propoxide and monoesters were obtained with 93% yield.

This modification of the Tishchenko reaction is especially catalyst dependent. With some catalysts traditional Tishchenko dimerization is a competitive reaction with this aldol-Tischenko variant. Villani and Nord have investigated the relationship between the basicity and Lewis acidity of the catalyst [82]. With Lewis acidic catalysts ($Al(OEt)_3$) only the dimeric ester is obtained whereas with more basic catalysts with low Lewis acidity (NaOEt) the glycol monoester is the only product [83]. If catalysts having both properties are used, e.g. $Mg[Al(OEt)_3]_2$ and $Ca(OEt)_2$ both reactions take place simultaneously. Tsuji et al. have studied this reaction over solid state catalysts and came to the same conclusion as Kuplinski and Nord in chapter 3.1.1. that the more basic the catalyst is the more favored aldol-Tishchenko reaction is [84].

In Addition to the traditional base catalysts, metal hydroxides and alcoholates, the trimerization of enolizable aldehydes to 1,3-glycol monoesters has also been catalyzed with several other metal catalysts. Polynuclear carbonyl-ferrates, e.g. $Fe3(CO)_{12}$ in pyridine or $Fe_3(CO)_{12}$-pyridine N-oxide in benzene induce trimerization of aliphatic aldehydes to 1,3-glycol monoesters with 95% overall yield [85]. Rather a large amount (33-73 mol%) of the catalyst is required and the reaction proceeds only with aldehydes that are not sterically hindered. Samarium complexes such as $Cp^*_2Sm(thf)_2$ catalyze the trimerization of several aliphatic aldehydes, eg. acetaldehyde to monoesters with 86% yield at r.t. in 1 hour. Thus, with SmI_2 the reaction does not occur at ambient temperature but at +50°C trimerization products were obtained with 74% yield [86]. Some Grignard reagents have also been reported to catalyze this particular reaction. A mixture of 2,4,6-trimethylphenoxymagnesium bromide and hexamethyl-phosphoric triamide (HMPT) (in the ratio 1 :1) gives a mixture of monoesters **7** and **83** when aliphatic, linear aldehydes are used [87]. This

system is also solvent dependent. The condensation products of the initial aldol step can be produced quantitatively if benzene is used instead of HMPT. Also higher HMPT catalyst concentrations, compared to the aldehyde, favor the condensation and yields of monoesters **7** and **83** are diminished [88]. The role of HMPT has been explained by its ability to coordinate the highly acidic cationic counter ion ($MgBr^+$) and depress its cationic properties [89]. On the other hand, in benzene such a coordination does not occur and the condensation reaction is favored to give α,β-unsaturated aldehydes.

4.2. HETERO ALDOL-TISHCHENKO REACTION

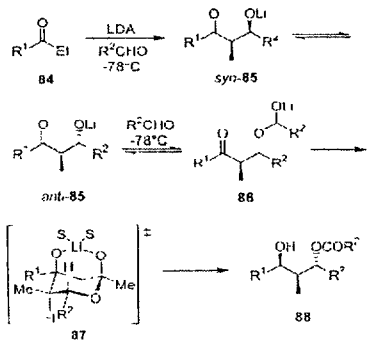
This particular modification has been under intensive research in recent years due to its excellent ability to form substituted *anti* 1,3-diol monoesters with excellent diastereoselectivities under mild conditions. The monoesters formed can be easily hydrolyzed to the corresponding 1,3-diols. In this reaction usually a ketone or aldehyde is used as a starting material with 2 equivalents of aldehyde over the catalyst. The importance of the reaction is due to a lack of the methods to create *anti* 1,3-diols especially in the synthesis of polypropianate type natural products where a 1,3-diol moiety is a typical part of their structure. There exist several methods for creating *syn* stereoselectivity like hydrogenation or reduction of aldol products. However, the number of methods to create *anti* selectivity is rare.

4.2.1. ENOLATES OF THE KETONES OR ALDEHYDES AS PRECURSORS

There are different ways to control the formation of the 1,3-diol monoesters and their stereoselectivity. The first one was the mixed Tischenko reaction where β-hydroxy aldehydes reacted with free aldehyde to monoester via 1,3-dioxan-4-ols. Another one, related to those, is the Evans-Tishchenko reaction where again the readily available β-hydroxyketone is used as the starting material. In order to avoid side reactions and get the reaction proceed selectively, one can also use enolates as the starting material with 200 mol% of free aldehyde. Here the enolate reacts immediately with the free aldehyde via aldol, followed with coordination of the second molecule of the free aldehyde to a bicyclic [6,6]-membered transition state. The hydride shift gives monoesters of 1,3-diols with good yields and excellent stereoselectivity. The monoesters formed can be hydrolyzed to the corresponding 1,3-diol functionality which is often a structural part of more complex natural products.

4.2.1.1. LITHIUM ENOLATE MEDIATED REACTIONS

The mechanism here is the same as reported in the Evans-Tishchenko reaction and has been investigated by many groups since Evans and Hoveyda in 1991. In the initial aldol reaction step both *syn* and *anti* isomers are formed and these lithium aldolates **85** form a hemiacetal **86** with another molecule of free aldehyde (Scheme 20) [90]. The excellent stereoselectivity of the Tishchenko step is due to the chair like transition state **87** in which alkyl substituents favor the equatorial orientation giving *anti*-diols as the main products after the hydride shift. In several studies aldol reactions are reported to be rever-



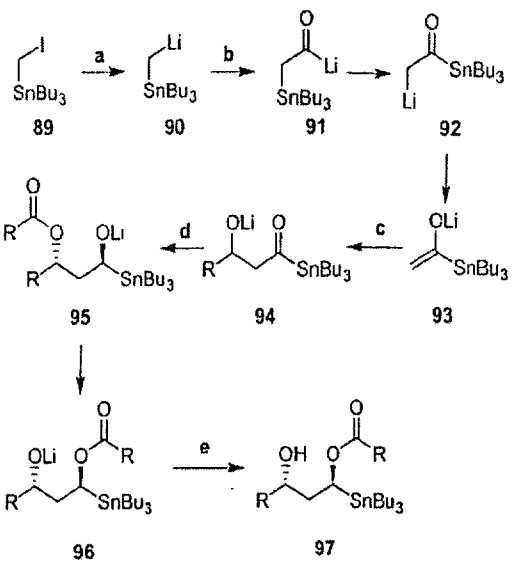
Scheme 20.

sible but Tishchenko reaction is irreversible. Additionally when lithium is used as a counter ion, some acyl migration can be obtained (10%).

Lithium enolates of ketones have been utilized in several cases in order to carry out similar stereoselective hetero aldol-Tishchenko reactions. The reaction mechanism, kinetics and the transition state have been studied by Streitwieser *et al.*, they concluded that the hydride shift is the rate determining step of the aldol-Tishchenko reaction [91]. This was studied in experiments where an isotope effect was observed and with computational studies.

A similar reaction has been carried out using α-haloketones as starting material [92]. Here this ketone is treated with different organometallic reagents like *n*-BuLi, PhMgBr, Et_2Zn, Me_3Al or Et_3B to create a reactive enolate via a metal-halogen exchange reaction. Thus, only BuLi was capable of affording the Tishchenko step for an aldolate like **85.** With other organometallic catalysts of that series only typical Reformatsky type products were obtained. The reaction system is also very solvent sensitive. When ether is used, the reaction proceeds well with good yields but in THF a complex product mixture can be obtained containing eg. the classical products of nucleophilic attack of the alkyl group of the reagent on the carbonyl carbon of the aldehyde or on the α-carbon bearing iodine. In hexane and toluene satisfactory yields of β-hydroxy ketones related to **88** are obtained with 71% and 56% yield, respectively. Differences in reaction temperature do not have a critical effect on the product distribution.

Iwamoto *et al.* have reported one optional way to produce a special acyltin enolate and its use in hetero aldol-Tishchenko disproportionation [93]. The acyltin enolate **93** is first generated from tributylstannylmethyliodide **89** by treatment of t-BuLi to give α-stannylmethyllithium **90** which reacts with carbon monoxide to acyllithium **91** and further smoothly undergoes anionic 1,2-stannyl rearrangement to the enolates of acyltin **92** and **93** (scheme 21). This acyltin enolate reacts



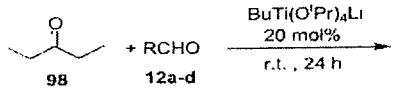
Scheme 21. Reactants and conditions: a) *t*-BuLi (2.2 eq.), Et_2O, -50°C, 10 min. b) CO (1 atm), -78°C, 2 h. c-d) RCHO (2.2 eq.), -78°C→20°C, 12 h. e) sat. NH_4Cl (aq), 20°C.

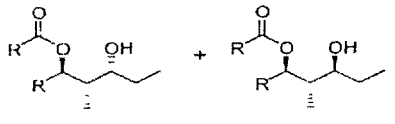
with the aldehyde to aldolate **94** and after formation of the acetal gives the Tishchenko product **95.** Thus, an intramolecular acyl migration (transfer of benzyl group) takes place to compound **96.** An acidic workup gives the final product **97** with 71% overall yield (R=Ph) or with 69% (R=^{i}Pr).

Thebtaranonth *et al.* have also reported an MPV reaction identical to the aldol-Tishchenko disproportionation to produce synthetically important epoxy-1,3-diol monoesters [94].

4.2.1.2. TITANIUM ENOLATE MEDIATED

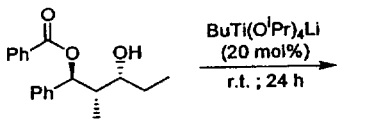
Some titanium complexes have been reported to be efficient catalysts in the aldol-Tishchenko reaction. The first one was reported by Mahrwald and Costisella with the titanium ate complex, $BuTi(O^iPr)_4Li$ [95]. In the presence of 20 mol% of the catalyst, ketone **98** undergoes aldol reaction with the aldehyde followed by Tishchenko esterification with another equivalent of aldehyde via a similar tran-





entry	R	Yield (%)	Ratio of 99 and 100
a	Ph	63	99 : 1
b	*t*-Bu	84	98 : 2
c	*i*-Pr	86	98 : 2
d	Pr	79	97 : 3

Scheme 22.

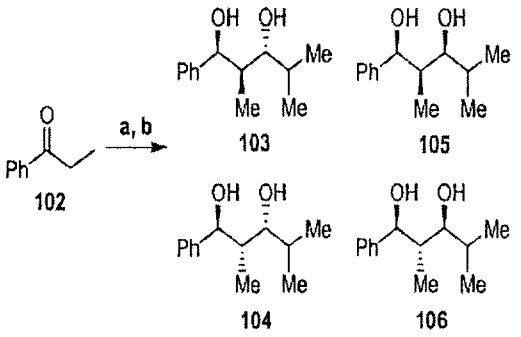


Scheme23. Acyl migration of 1,3-diol monoester

sition state as reported originally by Evans *et al.*, with SmI_2 [96]. The 1,3-diol monoesters **99** and **100** are obtained with good (63-86%) combined yield. Monoester **99** with *anti* 1,3-diastereoselecti-vity is obtained as the main product 97-99% (of **99** and **100**).

If monoester **99a** is treated over a catalytic amount of titanium ate complex, some acyl migration occurs to give isomerized monoester **101** (**1:2** / 90:10). Thus, this acyl migration is a slow process and dependent on the reaction time.

More recently Morken *et al.* reported that in the titanium ate complex system it is *i*-PrOLi which is formed and acts as the catalyst [97]. They tested the same system with *i*-PrOLi and obtained similar results in the hetero aldol-Tishchenko reaction as *Mahrwald et al.* obtained with their $BuTi(O^iPr)_4Li$ catalyst. Several simple metal alcoholates were also showed to achieve the same reaction with excellent *anti*-aldol/*anti*- Tishchenko ste-

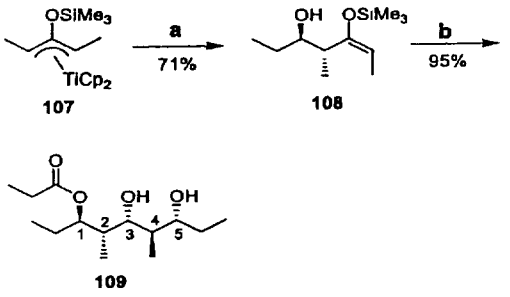


Scheme 24. Reagents and conditions: a) 20 mol% $M(OR)_n$, ^iPrCHO (2 equiv), 12 h. b) NaOH/MeOH.

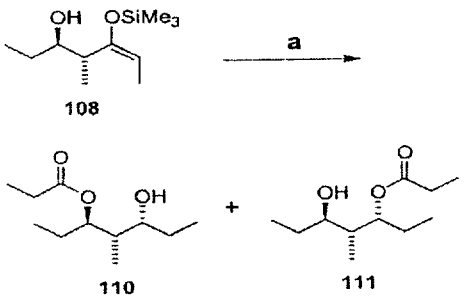
reoselectivity (Scheme 24). The monoesters of the 1,3-diols formed were hydrolyzed and analyzed as 1,3-diols. For example, LiO^iPr and NaO^tBu gave syn,anti-product **103** with excellent 99% and 98% diastereoselectivity respectively whereas with $La(O^iPr)_3$ only 4:1 selectivity was obtained after the ester methanolysis. Some *syn*-aldol/*anti*-Tishchenko product **104** was also obtained with low yield (1%). However, *syn*-Tishchenko products were formed in extremely low amounts.

Moïse *et al.* have reported Mukaiyama type titanium(IV)isopropoxide promoted tandem aldol-Tishchenko reactions concerning the synthesis of polypropionate derived natural products. Chiral silylated enolate **108** was first prepared by a highly stereoselective allyltitanation reaction from **107**. Mukaiyama type aldol-Tishchenko reaction (**108**→**109** in scheme 25) was then achieved to give 1,3-*anti* monoester **109** as the only product with excellent 95% yield and high stereoselectivity with five chiral centers [98].

With $Ti(O^iPr)_4$ the Tishchenko reaction is limited to small aldehydes. When the same reaction as described above (and in scheme 25)



Scheme 25. Reagents and conditions: a) EtCHO, -20°C. b) EtCHO (200 mol%), Ti(O^{i}Pr)4 (10 mol%), rt.



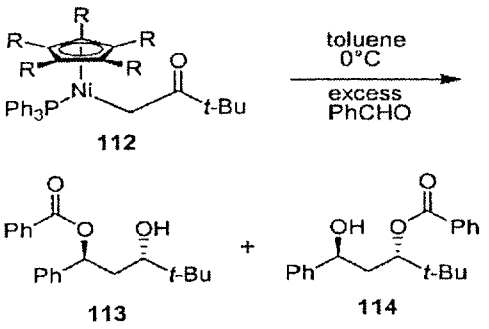
Scheme26. Reagents and conditions: a) TiCl2(O^{i}Pr)$_2$ (20 mol%), EtCHO, CH_2Cl_2, r.t.

is carried out with more bulky aldehydes eg. with α-branched ones, only the Mukaiyama aldol reaction occurs with high stereoselectivity but esterification can not be observed [99].

When silylenolate **108** is treated with $TiCl_2(O^iPr)_2$, the Mukaiyama aldol reaction does not take place but Tishchenko esterification gives the *anti* monoester of the 1,3-diol only with 95% yield (scheme 26). Again, acyl migration of product monoester **110** occurs to give isomeric monoester **111**.

4.2.1.3. TRANSITION METAL ENOLATES

Burkhardt *et al.* have reported aldol-Tishchenko reactions with nickel and palladium enolates such as $Cp(Ph_3P)NiCH_2COR$ **112** (Scheme 27) [100]. They reported these

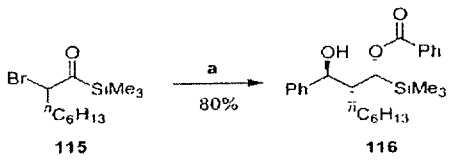


Scheme 27. Nickel enolate mediated Tishchenko reaction with benzaldehyde

catalysts as achieving self condensation of isobutyraldehyde, yielding monoesters **113** and **114**. Enolates similar to 112 achieve aldolreaction when treated with excess benzaldehyde in toluene at 0°C, and this is followed with Tishchenko esterification to esters 113 and 114 with 59-67% combined yield. The reaction is very temperature sensitive and the same reaction at room temperature and in benzene gives mainly α,β-unsaturated aldol condensation products. The corresponding palladium catalyst showed diminished reactivity for the same system.
Again here, monoester **113** is the first product but ester **114** is also observed via acyl migration. The ratio of these two esters depends on the reaction time, temperature and amount of the catalyst. The use of palladium instead of nickel makes the catalyst less active and the yields are decreased.

Also metallic zinc catalyses the aldol-Tishchenko reaction when α-haloacylsilane **115** is used in the presence of benzaldehyde [101]. Monoester **116** can be obtained as a single diastereomeric product with an 80 % yield. Here the zinc creates a zinc bromide type enolate of acylsilane which reacts first by aldol reaction with benzaldehyde to give the *anti*-adduct (scheme 28). The ZnBr-aldol adduct reacts further with the aldehyde to give this *syn,anti* product after acidic workup. The same reaction also proceeds with Et_2Zn and Me_3Ga with 87% and 95% yield, respectively.

Formation of **116** was also achieved with Me_3Al but with poor, 10%, yield.

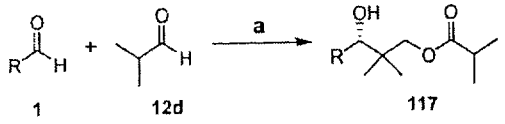


115 116

Scheme 28. reagents and conditions: a) Zinc dust, benzaldehyde (220 mol%).

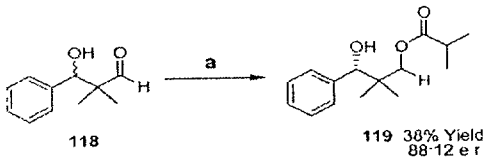
4.3. CHIRAL CATALYSTS IN ALDOL-TISHCHENKO

The effect of the chiral catalysts on the Aldol-Tishchenko reaction has been reported very lately by Morken et al., for the first time [102]. They used a chiral, substituted Y(II)Salen catalyst using $Y_5O(O^iPr)_{13}$ as a source of counter cation. They were also testing the reaction by using different aldehydes at the same time which is normally a very difficult situation to control.



1 12d 117

Scheme 29. Reagents and conditions:



118 119 38% Yield 88:12 e r

Scheme 30. Reagents and conditions: a) 2 mol% $Y_5O(O^iPr)_{13}$, 13 mol% ligand, ^iPrCHO (5 equiv.).

They also proved the effect of the chiral catalyst by using the same catalyst with racemic β-hydroxy aldehyde **118**. The Tishchenko reaction was obtained with a 38% yield and an enantiomer ratio of 88:12 (scheme 30). In time-course experiments it was also shown that the enantiomer ratio does not change as the reaction proceeds. They also reported a clear relationship between the enantiopurity of the ligand and the reaction enantioselectivity.

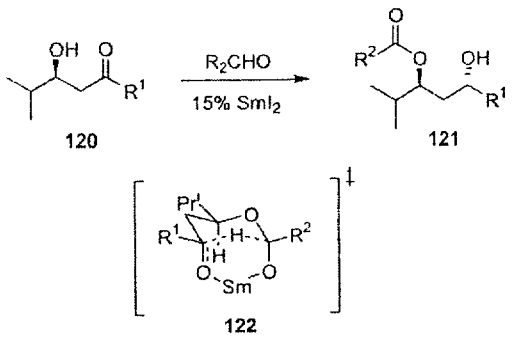
5. EVANS-TISHCHENKO REACTION

The structures of several natural products, especially polyketides, contain a 1,3-diol moiety. There exist a number of reductive methods to create such a *syn*-moiety from β-hydroxyketones (prepared easily by aldol reaction). On the other hand the methods for formation of the corresponding 1,3-diol *anti*-moiety are rare [103]. Even if some methods exist, the selectivities have varied from poor to good. Thus, monoester of *anti*-1,3-diol prepared with Evans-Tishchenko method, as well as with some modifications of aldol-Tishchenko method, can be easily hydrolyzed to *anti*-1,3-diol with excellent yields.

5.1. MECHANISM AND THE REACTION CONDITIONS

In 1990 Evans and Hoveyda published the reaction between β-hydroxyaldehyde **120** and a free aliphatic aldehyde where Tishchenko esterification takes place giving excellent *anti*-selectivity for the monoester of 1,3-diol **121** with excellent yields [96].They used SmI_2 as the catalyst at -10°C. The excellent stereoselectivity of the reaction is due to the [6+6] chairlike transition state **122** (scheme 31) formed. In this reaction formation of hemiacetal between the free aldehyde and β-hydroxyketone first takes place followed with coordination to the divalent samarium and then intramolecular hydride shift. The low reaction temperature of -10°C can probably promote the formation of hemiacetal and stabilize the transition state to give higher diastereoselectivities than higher temperatures.

The mechanism is similar to that presented earlier by Molander *et al.* in intramolecular Reformatsky type reaction [104]

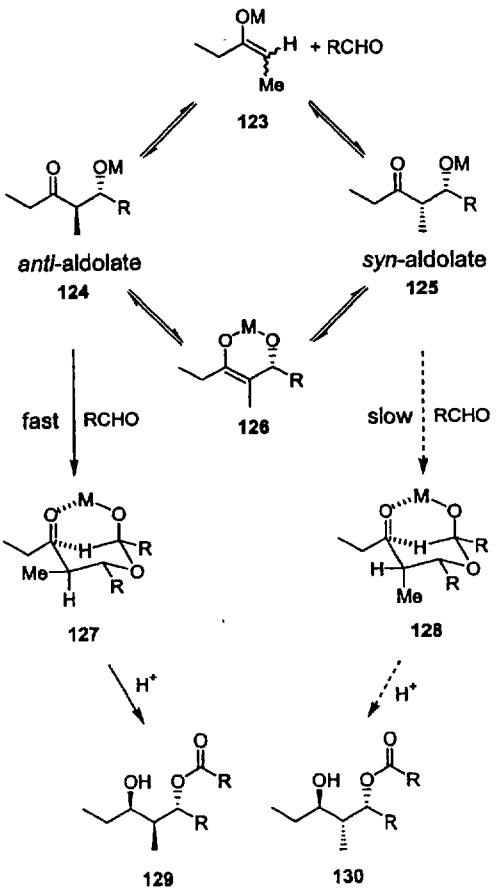


Scheme 31. Evans-Tishchenko reaction

and Meerwein-Ponndorf-Verley reduction / Oppenauer oxidation reactions catalyzed by SmI_2 [105]. A similar mechanism has been used to explain $Cp^*_2Sm(thf)_2$ catalyzed coupling reactions of vinyl esters with aldehydes to diesters [106]. This reaction is closely related to the Evans-Tishchenko reaction and its conditions.

Since then some other catalysts, like scandium triflate, $Sc(OTf)_3$, have been used successfully under similar conditions giving similar results though with slightly lower yields [107]. It should be noticed that as reactions proceed at higher temperatures (eg. in room temperature) the yields and a level of stereocontrol are reduced. As we reported in chapter 4 our investigations showed the formation of 1,3-dioxan-4-ol type 'double' hemiacetal to be temperature dependent and at least 0°C was required in order to reach complete formation of the desired hemiacetal. Regarding those results and the observations from $Sc(OTf)_3$ by Scott *et al.*, the temperature is probably playing a key role. Evans and Hoveyda have reported their studies with deuterium labeled aldehydes that hydride shift is not a rate determining step. They used an equimolar mixture of CH_3CHO and CD_3CDO and the product mixture contained products having H:D ratio of 1:1, which implicates that hydride transfer is rather fast and not rate limiting.

Lu *et al.* have studied a crossed aldol-Tishchenko reaction with SmI_2 in the presence of molecular sieves to produce *anti*-1,3-diol monoesters [108]. Molecular sieves have been used in order to facilitate the formation of SmI_2 and SmI_3. An advantage of lanthanide enolates in aldol reactions is their diminished basicity compared to alkali enolates which makes the aldol products formed more stable. This is probably also due to the intramolecular bidental co-ordination of e.g. samarium metal to the aldol product. They also studied the reasons for formation of only *anti-anti*-1,3-diol monoester. It is known that Lewis-acidic metal catalysts allow isomerisation of the enolates (Scheme 32.) and the aldol reaction to be reve-



Scheme 32

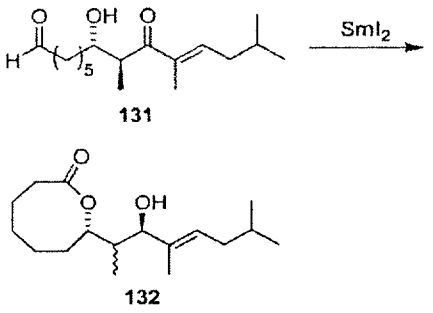
rsible. Lu *et al.* prepared a 1:1 mixture of *syn* and *anti* aldolates **124** and **125** (R=Ph, M=H) and added benzaldehyde (2.5 equiv) in the presence of SmI_2 (0.3 equiv) and molecular

sieves at 0°C for 0.5 hours. They obtained formation of *α,β-anti-β,γ-syn* 1,3-diol monoester **129** only, which indicates a rapid retroaldol and formation of *anti*-aldolate **124.** When isobutyraldehyde is used instead of benzaldehyde, both monoesters **129** and **130** were obtained but the amount of **129** increased faster as a function of time (**129:130** / 82:12 after 1 h at 0°C and 1 h at +22°C) which can also account for the retroaldol of *syn*-aldolate **125.** They concluded with the statement that Lewis-acidic catalyst (SmI_2 or titanium complex) can promote interconversion between *syn* and *anti* aldols. This interconversion is also facilitated with higher temperatures and is thus aldehyde dependent

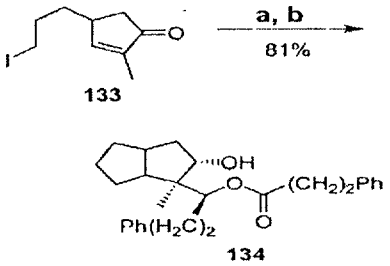
5.2. APPLICATIONS

Evans *et al.* have utilized this method in the synthesis of Bryostatin 2 fragments [109]. to produce the monoester of the 1,3-diol with excellent *anti*-stereoselectivity followed with hydrolysis to the *anti*-1,3-diol fragment. This method has been utilized successfully also e.g. in the synthesis of (-)-Rapamycin by Schreiber et al. [110], ansatrienine A by Kirschning et al. [111], and sphingosine and phytosphingosine by Schmidt and Wild [112]. The Evans-Tishchenko reaction has also been utilized successfully for several other purposes like ring closure studies towards Octalactin by Hulme *et al.* where 6-hydroxy aldehyde **131** was converted to lactone **132** in the presence of SmI_2 with good yield [113].

Several other catalysts have been utilized in the Evans-ishchenko reaction during the last decade showing that it is not samarium dependent. Several catalysts which were presented in the previous chapter, 'hetero aldol-Tishchenko reaction', can achieve the same reactions as presented here in the Evans-Tishchenko because the mechanism and the system is basically the same. (Ishii *et al.* have studied the correlation between different zirconocene complexes and aldehydes. In their studies 1,3-diol monoesters were observed with excellent yields and *anti*-selectivity with



Scheme 33. Intramolecular SmI_2 catalyzed ring closure



Scheme 34. Reagents and conditions: a) SmI_2 (2.5 equiv , 0.1M in THF), THF, DMPU (10 equiv), r.t., 5-15 min. b) $Ph(CH_2)_2CHO$ (200 mol%), r.t., 30-60 min

out any of the acyl migration that could be observed when $BuTi(O^iPr)_4Li$ was used as the catalyst.)

Curran *et al.* have achieved a similar Evans-Tishchenko reaction in a one pot system together with an initial vinylogous Barbier reaction [114]. The Barbier reaction of **133** first produces a bicyclic samarium enolate which further reacts by aldol reaction with dihydrocinnamaldehyde and then with Tishchenko reaction to monoester **134** with 81% yield and an excellent stereoselectivity to give only a single product. No aldol reaction between aldehydes was obtained. However, if there is no alkyl group in position 2 of *α,β*-unsaturated ketone **133,** some aldol condensation product can be obtained under similar conditions.

6. CONCLUSIONS

The Tishchenko reaction with its different modifications mentioned above offers an efficient tool for converting aldehydes to ester functionalities with excellent yields. The solutions of the reactions have been utilized and examined in recent decades increasingly intensively. With the use of different catalysts we can selectively steer the Tishchenko reaction to be proceed via desired way. Still there is much work in this area e.g. in studying the exact effects of different catalysts on the esterification in order to find out a clear link between the catalyst and the aldehydes used. We assume that studies with chiral catalysts in different modifications of the Tishchenko esterification will be under intensive research in the near future.

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