Highlight Review

The Tishchenko Reaction: A Classic and Practical Tool for Ester Synthesis

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Abstract

This article reviews the Tishchenko reaction: 2 RCHO → $RCOOCH_2R$ (R = hydrogen, alkyl, and aryl), describing the reaction mechanisms, homogeneous and heterogeneous catalysts developed for the reaction, a number of specific examples, and the utility of the reaction in the industrially large-scale production of ethyl acetate from acetaldehyde.

◆ Historical Background

The catalytic dimerization of aldehydes giving the corresponding esters (Scheme 1) was first discovered by Claisen in 1887,[1] and is now well known as "Tishchenko reaction." Claisen's method utilizing sodium alkoxides, however, was successfully applicable only to non-enolizable aldehydes like benzaldehyde, because sodium alkoxides that possess strong basicity catalyze aldol reactions predominantly for enolizable aldehydes with an α proton.

Scheme 1. Tishchenko reaction.

In 1906, a Russian chemist, Tischtschenko, reported that aluminum alkoxides were superior to sodium alkoxides in the reaction, because they were more Lewis acidic and less basic.[2] The Lewis acidic Al^{3+} ion with an empty orbital can effectively coordinate with a Lewis basic carbonyl oxygen atom of the reactant aldehyde. And more importantly, the lower basicity of aluminum alkoxides can suppress the undesirable aldol reactions and promote the Tishchenko reaction selectively. Taking advantage of these two features, aluminum alkoxides have been applied to the dimerization of not only non-enolizable but enolizable aldehydes to the corresponding esters with great success. Since Tischtschenko's method with aluminum alkoxides possesses much wider applicability than Claisen's method with sodium alkoxides, the dimerization of aldehydes to the corresponding esters has been named Tishchenko (Tischtschenko) reaction, even though the first person who found this type of reaction was Claisen.

Up to now, a number of homogeneous complex catalysts exhibiting high catalytic performances for the Tishchenko reaction have been elaborated to compensate for the shortcomings of the classical aluminum alkoxide catalysts. Heterogeneous catalytic Tishchenko reactions have been also achieved with activated solid bases and an immobilized complex, though the reports are few compared with those on homogeneous catalysis.

In view of synthetic organic chemistry, the Tishchenko reaction is one of the most ideal methods for preparation of esters and lactones, because the reaction requires no toxic reagents, proceeding catalytically without producing any byproducts. Some esters that can be synthesized through the Tishchenko reaction involve ethyl acetate from acetaldehyde and benzyl benzoate from benzaldehyde, which are important chemicals employed as a solvent and an artificial flavor.

In the present review, we focus on the traditional Tishchenko reaction and introduce all aspects of the reaction, including controversies on the reaction mechanism, both the homogeneous and heterogeneous catalysts developed so far, and its application to the industrially large-scale production of ethyl acetate from acetaldehyde.

◆ Homogeneous Catalysis Mechanism

The mechanisms that have been proposed for the traditional Tishchenko reaction catalyzed by metal alkoxides can be roughly divided into two groups; (1) Luder–Zuffanti model and (2) Ogata–Kawasaki model.

Luder and Zuffanti, in 1944, suggested a possible mechanism for the Tishchenko reaction, which was based on the hypothesis that aluminum alkoxide acts as an acid catalyst alone (Scheme 2).[3] This mechanism, however, was simplistically worked out according to the Lewis–Langmuir theory of valence, and possessed no experimental supports.

In 1969, Ogata and Kawasaki proposed a more reliable mechanism depicted in Scheme 3, in which [Al]–OCH_2R acts as the catalytically active species, on the basis of the experimental evidence that the alkoxide transfer from a catalyst to a reactant aldehyde is an indispensable step for the production of esters.[4] They stressed that aluminum alkoxide is essentially an alkoxide transfer agent to an aldehyde as well as a Lewis acid, and concluded that the Luder–Zuffanti model is incorrect. Since the Ogata–Kawasaki model is not a mere proposal but has much experimental support, it has been recognized as a correct mechanism of the Tishchenko reaction catalyzed by aluminum alkoxides.

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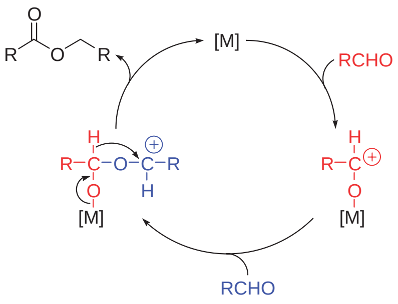
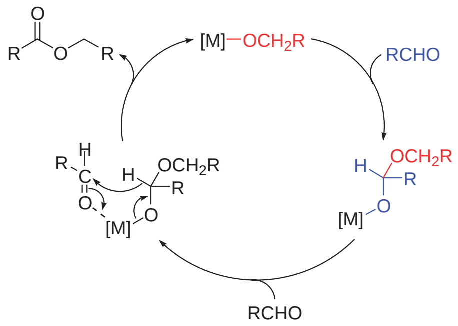


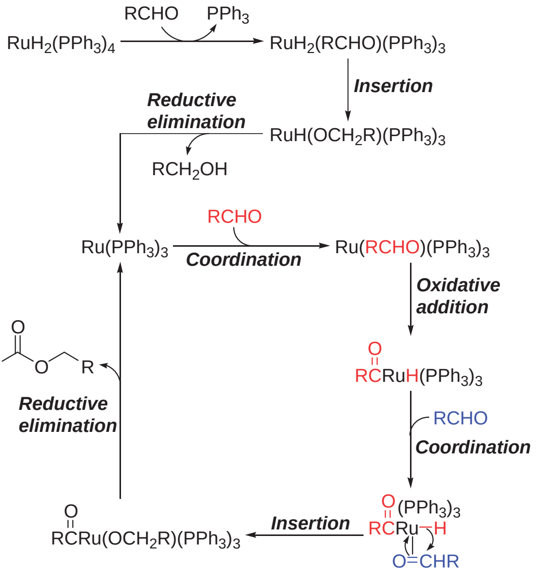
Scheme 2. Luder–Zuffanti model (M = Al^{3+}).



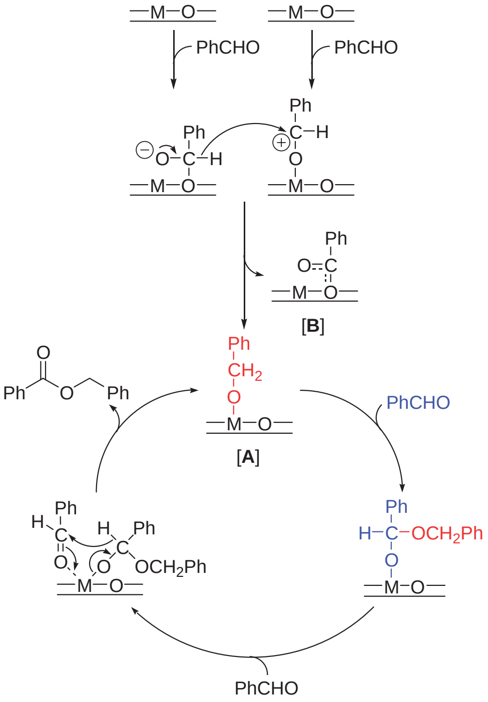
Scheme 3. Ogata–Kawasaki model (M = Al^{3+}).

In many cases, catalyst precursors of the newly elaborated catalysts have considerably different structures compared with traditional aluminum alkoxides. However, almost all of them as well as aluminum alkoxides are considered to be converted into the active species of $[M]–OCH_2R$ (M = metal; R = R of reactant aldehyde RCHO) through the initial reaction with reactant aldehydes.

We may have to consider another kind of mechanism for several transition-metal complex catalysts. There is a possibility that these catalysts promote the Tishchenko reaction by the mechanism involving oxidative addition, reductive elimination, insertion, and/or β-elimination. In 1982, Ito et al. proposed an interesting mechanism shown in Scheme 4 for the $RuH_2(PPh_3)_4$-catalyzed Tishchenko reaction.[5b] However, they could not rule out the possibility that $[Ru]–OCH_2R$ species was first formed and promoted the reaction via the Ogata–Kawasaki mechanism. In addition, no strong evidences supporting Scheme 4 have been obtained yet. Full elucidation of the transition metal-catalyzed Tishchenko reaction is one of the future subjects to be explored.



Scheme 4. Ito–Yamamoto model.



Scheme 5. Tanabe–Saito model (M = Mg^{2+} or Ca^{2+}).

◆ *Heterogeneous Catalysis Mechanism*

In 1974, Tanabe and Saito reported that alkaline earth oxides activated by thermal treatment induce the Tishchenko reaction of benzaldehyde, which is the first report of a heterogeneous catalytic Tishchenko reaction.[6] They proposed the mechanism shown in Scheme 5 for the Tishchenko reaction over MgO and CaO. The initial Cannizzaro-type disproportionation takes place between benzaldehyde adsorbed on an acid site and that on a base site to give the reduced adsorbed species [A] and oxidized one [B]. The former acts as a catalytically active species and promotes the reaction by way of the Ogata–Kawasaki mechanism. This mechanism was supported by the following results: (1) the decrease in activity upon addition of acidic compounds such as benzoic acid and phenol or basic pyridine indicates the participation of both base sites (O^{2-}) and Lewis acidic sites (Mg^{2+} or Ca^{2+}) in the reaction, (2) the existence of the oxidized and reduced adsorbed species on MgO and CaO was confirmed by infrared spectroscopy, and (3) the reaction over CaO had an induction period, which was shortened remarkably by the addition of benzyl alcohol. This is strong evidence for the participation of the reduced adsorbed species, $PhCH_2O–\underline{M}$ ($\underline{M}$ = Mg^{2+} or Ca^{2+}), in the catalytic production of benzyl benzoate; the abstraction of a proton in benzyl alcohol by a base site can yield

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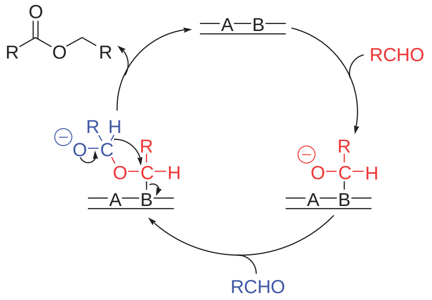


Scheme 6. Tsuji–Baba model (A = Lewis acid site; B = base site).

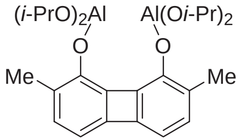
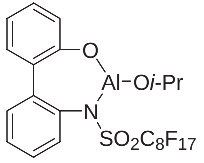
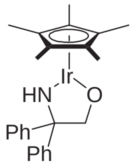
the same alkoxy species, which should take place much faster than the Cannizzaro-type disproportionation.

Tsuji and co-workers have proposed another mechanism for the Tishchenko reaction over activated metal oxides.[7] His recent report suggested that the surface lattice oxide ions in MgO, which act as active base sites, are incorporated into the product ester during the Tishchenko reaction.[7b] Baba and co-workers have also proposed the similar mechanism for KF/Al_2O_3-catalyzed Tishchenko reaction of benzaldehyde to benzyl benzoate, although there have been no decisive data supporting the suggestion (Scheme 6).[8]

◆ *Homogeneous Catalyst Examples*

The homogeneous catalysts developed so far for the Tishchenko reaction are listed in Table 1. As already described, the Tishchenko reaction was first performed by Claisen, using sodium alkoxides as homogeneous catalysts (Entry 1).[1]

Table 1. Homogeneous catalysts for the Tishchenko reaction

Entry	Catalyst	Ref(s)
	I. Group(1A)	
1	$NaOCH_3$	1
	II. Group(3B)	
2	$B(OH)_3$	9
3	$Al(OEt)_3$, $Al(Oi\text{-}Pr)_3$	2,10
4	$Al(OCH_2CCl_3)_3$, $Al(OCH_2CBr_3)_3$	11
5		12
6		13
7	$(i\text{-}Bu)_2AlH$ (DIBAH)	14
	III. Group(3A)	
8	$Cp^{*}_{2}LaCH(SiMe_3)_2$, $Cp^{*}_{2}NdCH(SiMe_3)_2$	15
9	$Y[N(SiMe_3)_2]_3$, $La[N(SiMe_3)_2]_3$, $Sm[N(SiMe_3)_2]_3$	16
	IV. Group(4A)	
10	Cp_2ZrH_2, Cp_2HfH_2	17
	V. Group(8)	
11	$Na_2Fe(CO)_4$	18
12	$K_2Fe(CO)_4$/18-crown-6	19
13	$RuH_2(PPh_3)_4$	5
14	$OsH_6(Pi\text{-}Pr_3)_2$, $OsH_2(CO)_2(Pi\text{-}Pr_3)_2$	20
15	$[Rh(diphosphine)(acetone)_2]^{+}$	21
16	 + i-PrOH + K_2CO_3	22

Stapp discovered that boric acid catalytically promotes the Tishchenko reaction, although a very high reaction temperature of 250 °C is required to obtain the product esters in a synthetically satisfactory yield (Entry 2).[9] Formaldehyde and isobutyraldehyde were converted into the corresponding esters in moderate yields in 6 h, but the reaction of benzaldehyde proceeded very slowly. An easily enolizable aldehyde, *n*-butyraldehyde, also underwent the Tishchenko reaction, although 2-ethyl-2-hexenal, an aldol condensate, was a predominant product. The Luder–Zuffanti mechanism (Scheme 2) was proposed for the reactions.

About twenty years after Tischtschenko's first report, Child and Adkins published the detailed catalysis of aluminum alkoxides for the Tishchenko reaction.[10] It was found that the catalytic activity for the reaction of acetaldehyde to ethyl acetate in xylene solvent at 25 °C increases in the order of $Al(OEt)_3 \ll Al(On\text{-}Bu)_3 < Al(Oi\text{-}Pr)_3$ and that the $Al(OEt)_3$-catalyzed reaction in CCl_4 proceeds faster than those in heptane, xylene, ether, benzene, and $CHCl_3$. They also showed that the use of promoters such as $FeCl_3$ and $ZnCl_2$ accelerates the $Al(OEt)_3$-catalyzed reaction of acetaldehyde in ether/butanol solvent at 25 °C.

Saegusa and Ueshima successfully performed the Tishchenko reaction of trihaloacetaldehydes such as Cl_3CCHO and Br_3CCHO, which had been reported to be very sluggish with traditional aluminum alkoxide catalysts, using $Al(OCH_2CX_3)_3$ (X = halogen) catalysts (Entry 4).[11] Their strategy was based on the previous NMR study, which had revealed that $[Al(OCH_2CX_3)_3]_n$ oligomers are easily dissociated into a monomeric form in the presence of such a donor as a reactant aldehyde, while the association of usual aluminum alkoxides such as $Al(OEt)_3$ and $Al(Oi\text{-}Pr)_3$ is strong and is not broken even by strong donors. They concluded that the smooth dissociation of $[Al(OCH_2CX_3)_3]_n$ oligomers into the active $Al(OCH_2CX_3)_3$ molecules brought about the remarkable acceleration of the reactions.

Maruoka and co-workers designed a unique bis-aluminum alkoxide depicted in Entry 5.[12] The carbonyl group of an aldehyde is coordinated to the two aluminum center at the same time, and thereby highly activated for the hydride transfer in the six-membered transition state shown in Scheme 3. The reaction of aliphatic aldehydes with the catalyst (0.2–1 mol %) usually proceeds very rapidly at 21 °C to yield the corresponding esters in more than 90% yield within 0.25 h. Aromatic aldehydes are somewhat less reactive in the catalytic system. In their succeeding work, they devised a novel catalyst shown in Entry 6, which is highly effective especially for the Tishchenko reaction of easily enolizable aldehydes.[13] It is remarkable that 1 mol % of the catalyst promoted the reaction of acetaldehyde quantitatively in 2 h at room temperature, indicative of the potential for the industrial production of ethyl acetate.

Hon and co-workers showed that a reducing agent, diisobutylaluminum hydride (DIBAH) promotes the Tishchenko reaction of aliphatic aldehydes at room temperature in several hours (Entry 7).[14] Unfortunately, aromatic aldehydes did not undergo the Tishchenko reaction with DIBAH. The Ogata–Kawasaki model was proposed as a reaction mechanism; the catalytically active species of $(i\text{-Bu})_2Al–OCH_2R$ should be formed by the initial reaction of DIBAH with an aldehyde RCHO.

Onozawa et al. found that $Cp^*{}_2LnCH(SiMe_3)_2$ (Ln = Nd or La) promotes the Tishchenko reaction of aromatic and heteroaromatic aldehydes, although the reaction is sluggish (Entry 8).[15] Usually operating the reaction at 60 °C for 3 days was required with 1 mol % of the catalysts to give the ester products in high yields. It was demonstrated that the reaction of $Cp^*{}_2LaCH(SiMe_3)_2$ with benzaldehyde yields $PhCOCH(SiMe_3)_2$, $PhCOCp^*$, and the [La]–OCH_2Ph species that was suggested to promote ester formation by the Ogata–Kawasaki mechanism. Later, Roesky et al. reported that $Ln[N(SiMe_3)_2]_3$ (Ln = Y, La, or Sm) also promotes the Tishchenko reaction by a similar mechanism (Entry 9).[16] The activity of $La[N(SiMe_3)_2]_3$, however, is much higher than those of $Cp^*{}_2LnCH(SiMe_3)_2$ catalysts.

Morita et al. found that a catalytic amount (5 mol %) of zirconocene and hafnocene complexes involving Cp_2ZrH_2, $Cp_2Zr(Cl)H$, Cp_2HfH_2, and $Cp_2Hf(Cl)H$ promote the Tishchenko reaction of aliphatic aldehydes at 0–17 °C, giving the corresponding esters in 42–92% yields within 0.5 h (Entry 10).[17] The catalysts, however, exhibited a low activity for the reaction of benzaldehyde. The ^1H NMR spectra of a 1:1 mixture of $Cp_2Zr(Cl)H$ and 2-methylpropanal or benzaldehyde indicated the formation of $Cp_2Zr(Cl)OCH_2CH(CH_3)_2$ or $Cp_2Zr(Cl)OCH_2Ph$, respectively. The formation of these alkoxy species during the Tishchenko reactions was also demonstrated by the fact that when Cp_2ZrH_2 or $Cp_2Zr(Cl)H$ was allowed to react with 2 equiv. of 2-methylpropanal, the product ester was obtained in 0 or 36% yield, respectively, while the same reaction employing only 5 mol % of the zirconium complexes yielded much higher yields. On the basis of the above results, the Ogata–Kawasaki model was proposed as a reaction path. They also suggested the possibility that the reaction involves a direct β-hydride elimination from the $Cp_2Zr(Cl)OCHROCH_2R$ intermediate to give the product ester of $RCOOCH_2R$ and $Cp_2Zr(Cl)H$, which is a catalytically active species.

Yamashita et al. reported that the anionic complex, $Na_2Fe(CO)_4$, which is known as the Collman reagent, promotes the catalytic Tishchenko reaction of aromatic aldehydes smoothly (Entry 11).[18] For instance, the treatment of 100 mmol of benzaldehyde with 3 mmol of the catalyst at 25 °C for 40 h in THF solvent gave benzyl benzoate in 95% yield. Owing to the highly basic nature of the catalyst, an easily enolizable aldehyde like *n*-butyraldehyde did not undergo the selective Tishchenko reaction, but afforded the corresponding aldol condensates. The reaction mechanism similar to the Tsuji–Baba model was proposed, where B̲ is [Fe(–II)] in this case, but they did not explain why a small amount of alcohol such as benzyl alcohol (ca. 3%) formed in the Tishchenko reaction of benzaldehyde. There is a possibility that [Fe]–OCH_2Ph species, which is formed by the initial reaction of $Na_2Fe(CO)_4$ with benzaldehyde, promotes the reaction through the Ogata–Kawasaki mechanism. In a later work, Yamashita et al. attempted to enhance the reactivity of $K_2Fe(CO)_4$ by adding 18-crown-6 that surrounds K^+ ions. The naked $Fe(CO)_4{}^{2-}$ with high nucleophilicity exhibited a much higher activity than $K_2Fe(CO)_4$ alone (Entry 12).[19]

Ito and co-workers used $RuH_2(PPh_3)_4$ and other hydridoruthenium complexes as catalysts for the Tishchenko reaction. These complexes were found to be active for aliphatic aldehydes involving acetaldehyde at −30–110 °C, but far less active for benzaldehyde (Entry 13).[5] The inhibitors and poisons for the catalysts involve carboxylic acids, alcohols, PPh_3, and pyridine. As already described, an interesting mechanism shown in Scheme 4 was proposed for the reaction catalyzed by $RuH_2(PPh_3)_4$. Recently, Barrio et al. reported that hydridoosmium complexes such as $OsH_6(P\textit{i}\text{-}Pr_3)_2$ and $OsH_2(CO)_2(P\textit{i}\text{-}Pr_3)_2$ are also usable for the Tishchenko reaction (Entry 14).[20] The Ito–Yamamoto model was suggested as a reaction mechanism.

Bergens et al. found that 1 mol % of a rhodium complex in the form of $[Rh(diphosphine)(acetone)_2]^+$ catalyzes the intramolecular Tishchenko reaction of both aromatic and aliphatic 1,4-dialdehydes at 34 °C to give the corresponding five-membered lactones (Entry 15).[21] The diphosphine ligands used were $Ph_2PCH_2CH_2PPh_2$ and $(C_6H_{11})_2PCH_2CH_2P(C_6H_{11})_2$. They proposed the Ito–Yamamoto model as a mechanism for the reactions.

Quite recently, Suzuki et al. developed an amino alcohol-based iridium bifunctional catalyst for the Tishchenko reaction (Entry 16).[22] The Tishchenko reaction of both enolizable aliphatic aldehydes and aromatic aldehydes proceeded smoothly in acetonitrile at room temperature with 1 mol % of the iridium catalyst and 20–30 mol % of K_2CO_3. The active species is considered to be the hydridoiridium complex formed by the reaction between the iridium complex depicted in Entry 16 and *i*-PrOH.

Coupled with an aldol reaction, a Tishchenko-like reaction of aromatic aldehyde has become a powerful tool for asymmetric synthesis of hydroxy esters with high optical purity. For example, the catalytic systems of $La(OTf)_3$–(*R*)-BINOL–BuLi[23] and $Ti(O\textit{t}\text{-}Bu)_4$–cinchonine[24] have been applied to the synthesis.

◆ *Heterogeneous Catalyst Examples*

Table 2 gives the heterogeneous catalysts developed so far for the Tishchenko reaction. The single component metal oxides and KF supported on alumina (KF/Al_2O_3) are solid base catalysts, and must be pre-activated by severe pretreatment at a high temperature (e.g., 773 K) under a high vacuum to generate strong basic surfaces with highly unsaturated metal–oxide or metal–

Table 2. Heterogeneous catalysts for the Tishchenko reaction

Entry	Catalyst	Ref(s)
	I. Single component metal oxides	
1	Alkaline earth oxides	6, 7, 25
2	γ-Al_2O_3	25d, 26
3	Mesoporous-Al_2O_3	26
4	Sulfated mesoporous-Al_2O_3	26
	II. KF supported on alumina	
5	KF/Al_2O_3	27
	III. Immobilized complex	
6	$Sm[N(SiMe_3)_2]_3$ supported on mesoporous silicate SBA-15	28

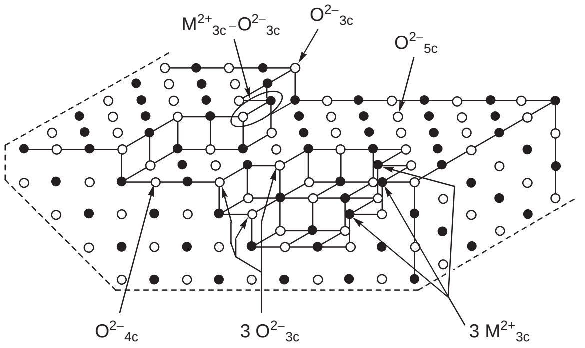


Figure 1. Surface model of the activated MgO (Ref. 30).

fluoride ion pairs that are the active sites for the Tishchenko reaction.[29] As a typical example of metal oxide catalysts, in Figure 1 is shown a surface model of the activated MgO that promotes the Tishchenko reaction.[30] The unsaturated Mg–O ion pairs appear by the high-temperature pretreatment under a high vacuum with the removal of H_2O, CO_2, and O_2 that are adsorbed on MgO in air at room temperature. The correlation between the coordination number of Mg–O ion pair and the activity of the ion pair for the Tishchenko reaction has not been elucidated yet.

Only benzaldehyde was used for the Tishchenko reaction in the first report on the use of alkaline earth oxides by Tanabe and Saito.[6] In succeeding works, activated alkaline earth oxides were also successfully applicable to the mixed Tishchenko reaction,[25c] the Tishchenko reaction of furfural that is difficult with homogeneous complex catalysts,[25a] and the intramolecular Tishchenko reaction of aromatic 1,2-dicarbaldehydes.[25b,25d]

Handa et al. first used KF/Al_2O_3 as a solid base catalyst in the Tishchenko reaction.[27a] The KF was loaded on Al_2O_3 by an impregnation method from the aqueous solution, followed by drying at 393 K for 12 h. Treatment of benzaldehyde with the KF/Al_2O_3 (KF content: $5\,\text{mmol g-alumina}^{-1}$) that had been pre-activated at 673 K under a vacuum (10^{-3} Pa) selectively gave the corresponding ester, benzyl benzoate, in 94% yield in 3 h at 323 K. It was revealed that the activity of KF/Al_2O_3 depends strongly upon the pretreatment temperature. Thus, careful setting of the pretreatment condition is required to achieve the highest catalytic performance. The active sites on KF/Al_2O_3 for base-catalyzed reactions including the Tishchenko reaction are still unknown, but the following reaction is considered to take place during the preparation of KF/Al_2O_3:

$$12KF + Al_2O_3 + 3H_2O \rightarrow 2K_3AlF_6 + 6KOH, \qquad (1)$$

where IR, XRD, and ^{19}F MAS NMR studies have revealed the formation of K_3AlF_6 species on the surface.[31] Ando and coworkers concluded that there exist three kinds of basic sites on KF/Al_2O_3; (i) well-dispersed and incompletely coordinated F^- ions, (ii) [Al–$\underline{\mathbf{O^-}}$] ions which give OH^- ions in the presence of H_2O, and (iii) [Al–$\underline{\mathbf{OH}}$] of which base strength is enhanced by the interaction of an adjacent F^- ion with the Al^{3+} as shown in Figure 2.[32] If this suggestion is correct, one or more than one of the base sites promote the Tishchenko reaction.

Chen et al. prepared an immobilized samarium catalyst through the reaction of $Sm[N(SiMe_3)_2]_3$ with mesoporous silicate SBA-15 (Entry 6, Figure 3).[28] The immobilization renders work-up procedures quite easy, improving the reusability and the stability toward oxygen. The immobilized catalyst is usable for aromatic aldehydes, giving the corresponding esters in moderate to high yields, although the activity was somewhat lower than that of the parent $Sm[N(SiMe_3)_2]_3$ catalyst.

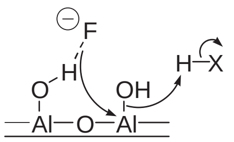


Figure 2. Cooperative basicity of F^- and alumina. HX is a Brønsted acidic molecule.

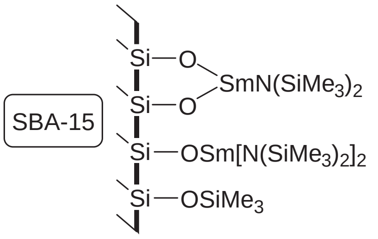
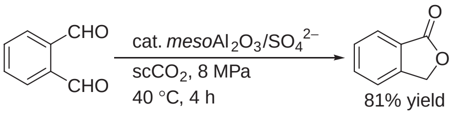


Figure 3. Surface model of the immobilized catalyst (Ref. 28).



Scheme 7. Intramolecular Tishchenko reaction in $scCO_2$ using sulfated mesoporous alumina (*meso*$Al_2O_3/SO_4{}^{2-}$) as a solid strong base catalyst.

The Tishchenko reaction in supercritical CO_2 ($scCO_2$), which is an ideal reaction medium in view of *green chemistry*,[33] has been also achieved with heterogeneous catalysts. We have recently found that activated alumina and mesoporous alumina, especially those modified with sulfate ions, show high activities for the intramolecular Tishchenko reaction of phthalaldehyde to phthalide in $scCO_2$ (Scheme 7).[26] It was demonstrated that active strong base sites on the catalysts are not neutralized even in the Lewis acidic $scCO_2$ medium and effectively promote the reaction.

◆ *Tishchenko Reaction in Industry*

Transformation of acetaldehyde into ethyl acetate is the sole practical application of the Tishchenko reaction to large-scale production of bulk chemicals in the chemical industry.

A catalyst of $Al(OEt)_3$[34a] and a co-catalyst of $ZnCl_2$ are mixed with acetaldehyde in ethyl acetate solvent at 0–5 °C in a tubular reactor to produce ethyl acetate in 95–97% yield and over 99.5% selectivity.[34b] Since the reaction is exothermic, maintaining the low reaction temperature is required to suppress a side reaction like the aldol condensation of acetaldehyde.[34c] In countries where cheap ethanol is available, the ester formation from acetic acid and ethanol is advantageous. However, in Germany and Japan where an ample supply of acetaldehyde is available and/or the price of ethanol is expensive owing to her taxation policy, the performance of the Tishchenko reaction becomes predominant in the formation of ethyl acetate. In

2005, 1.5 million tons of ethyl acetate was produced worldwide, and approximately one third of the production was dependent on the Tishchenko route. A global demand for ethyl acetate is currently increasing as an alternative solvent to aromatics like toluene.

♦ Summary

As mentioned earlier, the Tishchenko reaction was discovered more than one hundred years ago. Up to now, a variety of types of catalysts have been developed in light of homogeneous and heterogeneous catalysis. It should be underscored that the catalytic cycle of the Tishchenko reaction includes mild oxidation–reduction processes, and the formation of an ester from two molecules of aldehyde is a 100% *atom economy* reaction.

It is also amazing to see that the Tishchenko reaction of acetaldehyde to ethyl acetate is selectively performed in the chemical industry, while suppressing the competitive aldol condensation of such an easily enolizable aliphatic aldehyde with α hydrogens.

References and Notes

T.S. is a Research Fellow of the Japan Society for the Promotion of Science.

1 L. Claisen, *Ber.* **1887**, *20*, 646.

2 a) W. Tischtschenko, *J. Russ. Phys. Chem.* **1906**, *38*, 355. b) W. Tischtschenko, *Chem. Zentralbl.* **1906**, *77I*, 1309.

3 W. F. Luder, S. Zuffanti, *Chem. Rev.* **1944**, *34*, 345.

4 Y. Ogata, A. Kawasaki, *Tetrahedron* **1969**, *25*, 929.

5 a) H. Horino, T. Ito, A. Yamamoto, *Chem. Lett.* **1978**, 17. b) T. Ito, H. Horino, Y. Koshiro, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504.

6 K. Tanabe, K. Saito, *J. Catal.* **1974**, *35*, 247.

7 a) H. Tsuji, F. Yagi, H. Hattori, H. Kita, *J. Catal.* **1994**, *148*, 759. b) H. Tsuji, H. Hattori, *ChemPhysChem* **2004**, *5*, 733.

8 a) T. Baba, *Catal. Surv. Jpn.* **2000**, *4*, 17. b) Y. Kawanami, H. Yuasa, F. Toriyama, S.-I. Yoshida, T. Baba, *Catal. Commun.* **2003**, *4*, 455.

9 P. R. Stapp, *J. Org. Chem.* **1973**, *38*, 1433.

10 W. C. Child, H. Adkins, *J. Am. Chem. Soc.* **1925**, *47*, 798.

11 T. Saegusa, T. Ueshima, *J. Org. Chem.* **1968**, *33*, 3310.

12 a) T. Ooi, T. Miura, K. Takaya, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 7695. b) Review of the bidentate Lewis acid catalysts: K. Maruoka, *Catal. Today* **2001**, *66*, 33.

13 T. Ooi, K. Ohmatsu, K. Sasaki, T. Miura, K. Maruoka, *Tetrahedron Lett.* **2003**, *44*, 3191.

14 Y. Hon, C. Chang, Y. Wong, *Tetrahedron Lett.* **2004**, *45*, 3313.

15 S. Onozawa, T. Sakakura, M. Tanaka, M. Shiro, *Tetrahedron* **1996**, *52*, 4291.

16 a) H. Berberich, P. W. Roesky, *Angew. Chem., Int. Ed.* **1998**, *37*, 1569. b) M. R. Bürgstein, H. Berberich, P. W. Roesky, *Chem. Eur. J.* **2001**, *7*, 3078.

17 K. Morita, Y. Nishiyama, Y. Ishii, *Organometallics* **1993**, *12*, 3748.

18 M. Yamashita, Y. Watanabe, T. Mitsudo, Y. Takegami, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3597.

19 M. Yamashita, T. Ohishi, *Appl. Organomet. Chem.* **1993**, *7*, 357.

20 P. Barrio, M. A. Esteruelas, E. Onate, *Organometallics* **2004**, *23*, 1340.

21 S. H. Bergens, D. P. Fairlie, B. Bosnich, *Organometallics* **1990**, *9*, 566.

22 T. Suzuki, T. Yamada, T. Matsuo, K. Watanabe, T. Katoh, *Synlett* **2005**, 1450.

23 V. Gnanadesikan, Y. Horiuchi, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 7782.

24 K. Rohr, R. Herre, R. Mahrwald, *Org. Lett.* **2005**, *7*, 4499.

25 a) T. Seki, K. Akutsu, H. Hattori, *Chem. Commun.* **2001**, 1000. b) T. Seki, H. Hattori, *Chem. Commun.* **2001**, 2510. c) T. Seki, H. Kabashima, K. Akutsu, H. Tachikawa, H. Hattori, *J. Catal.* **2001**, *204*, 393. d) T. Seki, H. Tachikawa, T. Yamada, H. Hattori, *J. Catal.* **2003**, *217*, 117.

26 a) T. Seki, M. Onaka, *Chem. Lett.* **2005**, *34*, 262. b) T. Seki, M. Onaka, *J. Phys. Chem. B* **2006**, *110*, 1240.

27 a) H. Handa, T. Baba, H. Sugisawa, Y. Ono, *J. Mol. Catal. A: Chem.* **1998**, *134*, 171. b) H. Kabashima, H. Tsuji, S. Nakata, Y. Tanaka, H. Hattori, *Appl. Catal., A: Gen.* **2000**, *194–195*, 227.

28 Y. Chen, Z. Zhu, J. Zhang, J. Shen, X. Zhou, *J. Organomet. Chem.* **2005**, *690*, 3783.

29 H. Hattori, *Chem. Rev.* **1995**, *95*, 537.

30 S. Coluccia, A. J. Tench, *Proceedings of the 7th International Congress on Catalysis*, Tokyo, Japan, **1980**, p. 1160.

31 a) C. V. A. Duke, J. M. Miller, J. H. Clark, A. P. Kybett, *J. Mol. Catal.* **1990**, *62*, 233. b) L. M. Weinstock, J. M. Stevenson, S. A. Tomellini, S.-H. Pan, T. Utne, *Tetrahedron Lett.* **1986**, *27*, 3845.

32 a) T. Ando, J. H. Clark, D. G. Cork, T. Hanafusa, J. Ichihara, T. Kimura, *Tetrahedron Lett.* **1987**, *28*, 1421. b) T. Ando, *Acid-Base Catalysis II*, Kodansha-Elsevier, Tokyo, **1994**, p. 9.

33 a) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, *99*, 475. b) T. Ikariya, Y. Kayaki, *Catal. Surv. Jpn.* **2000**, *4*, 39. c) A. Baiker, *Chem. Rev.* **1999**, *99*, 453. d) J.-D. Grunwaldt, R. Wandeler, A. Baiker, *Catal. Rev. Sci. Eng.* **2003**, *45*, 1. e) J.-D. Grunwaldt, A. Baiker, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3526.

34 a) D. Ulrich, H. Jankowski, *Chem. Tech.* **1988**, *40*, 393. b) K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*, 4th ed., Wiley-VCH, Weinheim, **2003**. c) A. S. Hester, K. Himmler, *Ind. Eng. Chem.* **1959**, *51*, 1424.