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Synthesis of phthalide–skeleton using selective intramolecular Tishchenko reaction over solid base catalysts

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Abstract

An efficient, economical, and environmentally benign method for the synthesis of phthalide–skeleton using heterogeneous catalytic intramolecular Tishchenko reaction with solid bases is described. Among the solid base catalysts examined, MgO, CaO, and SrO exhibited high catalytic performances for the intramolecular Tishchenko reaction of *o*-phthalaldehyde to yield phthalide exclusively in excellent yields at 313 K in the short time span of 0.25 h. Application of γ-alumina to the intramolecular Tishchenko reaction of *o*-phthalaldehyde was also successful; phthalide was obtained selectively in excellent yields at 313 K in 4 h. The employment of KF/alumina and KOH/alumina at 313 K for 4 h resulted in the selective formation of phthalide in moderate yields. The heterogeneous catalytic systems realized by the use of CaO and γ-alumina were also successfully applicable to the selective intramolecular Tishchenko reaction of 2,3-naphthalenedicarbaldehyde to give the corresponding five-membered lactone in excellent yields at 333 K for 2 and 20 h, respectively. Based on the reaction results, the infrared spectra of adsorbed *o*-phthalaldehyde, and the quantum chemical calculations conducted at the PM3-MO level of theory for elucidation of the molecular and electronic structures of *o*-phthalaldehyde and the potential intermediates, a plausible reaction mechanism for the intramolecular Tishchenko reaction of *o*-phthalaldehyde to phthalide over MgO and γ-alumina was proposed. The catalytically active species should be *o*-$MOCH_2C_6H_4CHO$ ($M = $ Mg or Al).

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Keywords: Solid base catalyst; Intramolecular Tishchenko reaction; Lactonization; 1,4-Dialdehydes; Phthalides

1. Introduction

The surface of the materials called solid base or heterogeneous base, when activated at high temperature under high vacuum, provides a powerfully polarized environment with the generation of highly unsaturated surface atoms induced by the removal of carbon dioxide, water, and, in some cases, oxygen from the surface. Such a high polar surface field, which contains not only basic sites but also acidic sites, has been applied to many ionic and heterolytic organic reactions with great success [1].

One of the most interesting organic catalytic reactions that proceeded efficiently over solid bases is the Tishchenko reaction which involves a dimerization of aldehydes yielding the corresponding esters initiated by the interactions of polarized carbonyl groups of aldehydes with surface acidic and basic sites of solid bases [1,2]. A classical Tishchenko reaction used to be conducted in homogeneous catalytic systems realized by aluminum alkoxides [3]. To improve activity and selectivity, however, several organometallic complexes have been elaborated for homogeneous catalytic reaction. Recent articles dealing with homogeneous catalyses realized by the use of organometallic complex catalysts have reported considerable improvements in activities for the dimerization of aldehydes in comparison with traditional aluminum alkoxide catalysts [4b–h]. Solid base catalysts, unlike those homogeneous catalysts, can be easily separated from the reaction mixture after the reaction is carryied out and are inexpensive and environmentally benign. These excellent advantages emphasize the importance of the replacement of the homogeneous catalysts with the heterogeneous catalysts both in the laboratory and in the industrial processes utilizing Tishchenko esterification.

The Tishchenko reaction, when carried out with dialdehydes, can be an efficient method for preparation of lactones via the intramolecular catalytic esterification [4d,4f–h,5].

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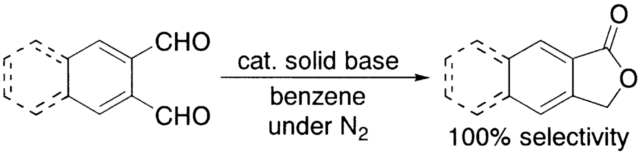


Scheme 1. Selective intramolecular Tishchenko reaction yielding phthalide–skeleton over solid base catalysts.

We have also attempted this approach employing alkaline earth oxides (MgO, CaO, and SrO) and successfully realized heterogeneous catalytic intramolecular Tishchenko reaction of *o*-phthalaldehyde to phthalide [2f]. Phthalide–skeletons are often contained in pharmaceuticals and natural products exhibiting important biological activities [6a,6b,6e,6g–j]. In addition, they are employed as important precursors for the synthesis of various compounds with more complicated structures [6c,6d,6f,6h–k]. Thus, the demand for nontoxic and practical catalytic systems for the preparation of phthalide–skeleton will further increase both in laboratory and in industry. As one of the potential responses to such a demand, here, we present a full account of our new approach to phthalide–skeleton synthesis using an intramolecular Tishchenko reaction with environmentally benign, economical, and highly effective solid base catalysts (Scheme 1).

2. Experimental

2.1. Catalysts

Magnesium oxide, CaO, SrO, and BaO were prepared from $Mg(OH)_2$, $Ca(OH)_2$, $SrCO_3$, and $BaCO_3$, respectively, by thermal decomposition at elevated temperatures in vacuo for 2 h. JRC-ALO-1A, 2, 3, 4, and 5A (aluminas of the reference catalysts of the Catalysis Society of Japan) were supplied from the Catalysis Society of Japan and contained the following impurities: JRC-ALO-1A, 0.02%Fe_2O_3, 0.01%SiO_2, 0.03%Na_2O; JRC-ALO-2, 0.03%Fe_2O_3, 0.22%SiO_2, 0.04%Na_2O, 1.72%SO_4^{2-}; JRC-ALO-3, 0.01%Fe_2O_3, 0.01%SiO_2, 0.3%Na_2O, 0.01%TiO_2; JRC-ALO-4, 0.01%Fe_2O_3, 0.01%SiO_2, 0.01%Na_2O; JRC-ALO-5A, 0.76%Fe_2O_3, 0.03%Na_2O, a trace of SO_4^{2-} (< 0.01%). Potassium fluoride supported on alumina (KF/alumina) was purchased from Fluka Chemical Co., and its content of KF was determined to be 8.2 $\mathrm{mmol\,g^{-1}}$ by X-ray fluorescence. Potassium hydroxide supported on alumina (KOH/alumina) was prepared by impregnation of γ-alumina (JRC-ALO-4) with an aqueous solution of KOH, followed by drying at 373 K in air. The content of KOH was 1.2 $\mathrm{mmol\,g^{-1}}$. Hydrotalcite ($Mg/Al = 2$) was synthesized as reported [7]. Lanthanum oxide was prepared from $La(OH)_3$ using the same procedures as those for alkaline earth oxides, where $La(OH)_3$ was obtained from an aqueous solution of $La(NO_3)_3$ by hydrolysis with an aqueous ammonia, followed by washing with distilled water and drying at 373 K. Zirconium oxide and ZnO were prepared from $Zr(OH)_4$ and $Zn(OH)_2$, respectively, by the same procedures as those for alkaline earth oxides. The surface areas of the above solid bases were determined by applying the BET equation to the nitrogen adsorption at 77 K.

2.2. Reactants and solvents

Dialdehydes (**1** and **3**) and solvents (benzene and tetrahydrofuran) were purchased from Aldrich Chemical Co. Solvents were purified by passage through molecular sieve 4A under a reduced pressure to remove water and carbon dioxide exclusively.

2.3. Reaction procedures

To a Schlenk tube containing a solid base pretreated at an elevated temperature in vacuo for 2 h was added a benzene solution of dialdehyde under N_2 at room temperature. Then the reaction mixture was warmed to a certain reaction temperature and stirred for a prescribed reaction time. The resulting solution, after the solid base was separated, was analyzed by GC equipped with a column of DB-1 (total length, 60 m; diameter, 0.25 mm) to determine the yield (%) of the product lactone. The products were identified by ^{1}H–NMR and GC–MS analyses based on previous reports [4d, 4h,5].

2.4. Measurement of infrared spectra

Thin disks of $Mg(OH)_2$ and γ-alumina (JRC-ALO-4) prepared by pressing were pretreated at 873 and 773 K, respectively, in vacuo for 2 h in a quartz-made glass tube equipped with the optical path. *o*-Phthalaldehyde was adsorbed on the disks at room temperature. Desorption of *o*-phthalaldehyde and phthalide from the disks was carried out by successive evacuation at room temperature, 473, 573, and 673 K for 20 min at each temperature. Infrared spectra were measured at room temperature with a Perkin–Elmer spectrum one FT–IR spectrometer equipped with a MCT detector.

2.5. Quantum chemical calculations

Quantum chemical calculations were carried out at the PM3–MO level of theory [8]. A cluster model composed of $(MgO)_{16}$ was used in the calculations. The cluster model and all adsorption structures were fully optimized by means of the PM3 energy gradient method.

3. Results and discussion

3.1. Activities of solid base catalysts for the intramolecular Tishchenko reaction of o-phthalaldehyde to phthalide

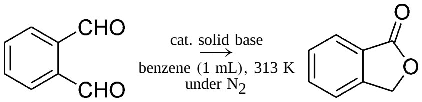
The conversion of *o*-phthalaldehyde (**1**) to phthalide (**2**) has been employed as a common standard reaction in the studies of the intramolecular Tishchenko reaction and successfully performed in the homogeneous catalytic systems realized by the use of a series of complexes of the type $[Rh(diphosphine)(solvent)_2]^+$ (solvent = weakly coordinating solvent) [5], $K_2[Fe(CO)_4]$-crown ether [4d], lanthanoid complexes such as $(C_5Me_5)_2LaCH(SiMe_3)_2$ and $La[N(SiMe_3)_2]_3$ [4f,4h], and bidentate aluminum alkoxides [4g], although the reaction mechanisms are considerably different. Thus, we chose the catalytic conversion of **1** to **2** with solid bases as a representative reaction. The activities of solid base catalysts for the intramolecular Tishchenko reaction of **1** to **2** are listed in Table 1. With the intention of comparing the activities of solid base catalysts, 1 mmol of **1** was treated with 10 mg of each solid base at 313 K for 1 h. In addition, the reactions with MgO, CaO, SrO, γ-alumina, KF/alumina, and KOH/alumina were performed under appropriate conditions that gave **2** in synthetically satisfactory level of yields.

Although the employment of BaO was unsuccessful and resulted in total recovery of the starting material, the other alkaline earth oxides, MgO, CaO, and SrO, were all successfully applied to the intramolecular Tishchenko reaction of **1** to **2**. A comparative approach conducted by the treatment of 1 mmol of **1** with 10 mg of MgO, CaO, and SrO in 1 mL of benzene at 313 K for 1 h led to a conclusion that the activities of MgO and SrO are almost equal and moderate (entries 1 and 6), while that of CaO is remarkably high (entry 4). Increasing the catalyst weight of MgO, CaO, and SrO from 10 to 50 mg without changing the other reaction conditions accomplished the formation of **2** in excellent yields in a short timespan of 0.25 h (entries 2, 5, and 7). It should be noted that MgO, CaO, and SrO yielded **2** exclusively, namely, by products including the intermolecular Tishchenko products were not detected by GC–MS analysis. These results clearly demonstrate the high adaptability of MgO, CaO, and SrO to the catalytic conversion of **1** to **2**.

In contrast to a number of successful applications of γ-alumina to catalyst supports, γ-alumina in itself has been used in organic synthesis with very limited success [1,9]. In addition, because of the low activity, γ-alumina often requires extremely high reaction temperatures, which results in irreparable damage to the reactant molecule with poor thermostability [1a,9]. The intermolecular Tishchenko reaction as well has been reported to be difficult in γ-alumina-catalyzed reaction when *n*-butyraldehyde, benzaldehyde, pivalaldehyde, and furfural were used as reactants [2a–e,2g, 4a]. Surprisingly, however, treatment of **1** with γ-alumina (aluminas of the reference catalysts of the Catalysis Society of Japan) under otherwise similar or much milder reaction conditions compared with the above reports [2a–e,2g, 4a] afforded **2** exclusively in good to excellent yields (entries 9–11, 13, and 15). Among the catalysts tested, JRC-ALO-3 containing the largest amount of Na_2O impurity that reduces the number of acidic sites (Al^{3+}) remarkably [1a] exhibited the lowest activity, implying that acidic sites (Al^{3+}) participate in the catalytic conversion of **1** to **2**. The result that JRC-ALO-2 possesses the largest number of acidic sites (Al^{3+}) because the largest amount of $SO_4{}^{2-}$ and SiO_2 impurities [1a] furnished **2** in the highest yield (99%) also emphasizes the participation of acidic sites (Al^{3+}) in the present Tishchenko lactonization. The activity of γ-alumina for the lactonization of **1** to **2** was lower than that of MgO, CaO, and SrO; γ-alumina requires a longer reaction time than MgO, CaO, and SrO to achieve a synthetically satisfactory level of yield.

Although the surface chemical property is still cloaked in secrecy, KF supported on alumina (KF/alumina) has been employed as a solid base catalyst or a solid base reagent in a number of organic reactions with great success [1b–d,9]. The applications of KF/alumina to the Tishchenko reactions of

Table 1
Heterogeneous catalytic intramolecular Tishchenko reaction of *o*-phthalaldehyde (**1**) to phthalide (**2**) with solid bases



1
(1 mmol)
2

Entry	Catalyst	Catalyst weight (mg)	Pretreatment temperature (K)	Surface area[a] (m^2/g)	Reaction time (h)	Yield[b] (%)
1	MgO	10	873	267	1	15
2	MgO	50	873	267	0.25	91
3[c]	MgO	50	873	267	0.25	87
4	CaO	10	873	48	1	59
5	CaO	50	873	48	0.25	quant.
6	SrO	10	1273	12	1	15
7	SrO	50	1273	12	0.25	86
8	BaO	10	1273	2	1	0
9	ALO-1A	50	773	172	4	83
10	ALO-2	50	773	312	4	99
11	ALO-3	50	773	129	4	68
12	ALO-4	10	773	173	1	8
13	ALO-4	50	773	173	4	93
14[c]	ALO-4	50	773	173	4	62
15	ALO-5a	50	773	250	4	98
16	KF/alumina	10	673	40	1	5
17	KF/alumina	50	673	40	4	35
18	KOH/alumina	10	873	160	1	3
19	KOH/alumina	50	873	160	4	53
20	Hydrotalcite	10	673	118	1	0
21	La_2O_3	10	873	33	1	< 1
22	ZrO_2	10	873	42	1	0
23	ZnO	10	873	2	1	0

[a] Determined by BET method.
[b] Determined by GC equipped with a column of DB-1.
[c] Tetrahydrofuran (1 mL) was used as solvent.

benzaldehyde and pivalaldehyde have been also performed successfully [2c,2d]. When the reaction was carried out in 1 mL of benzene at 313 K for 1 h using 1 mmol of **1** and 10 mg of KF/alumina as a reactant and a catalyst, respectively, **2** was obtained exclusively in a yield of 5% (entry 16). Increasing the catalyst weight from 10 to 50 mg and extending the reaction time from 1 to 4 h enhanced the yield of **2** to 35% (entry 17).

Potassium hydroxide supported on alumina (KOH/alumina) exhibited activity for the catalytic conversion of **1** to **2** and yielded **2** selectively in a moderate yield of 53% when 1 mmol of **1** was treated with 50 mg of KOH/alumina in 1 mL of benzene at 313 K for 4 h (entry 19). This result was somewhat surprising because KOH/alumina has been reported to be an almost inert catalyst for the Tishchenko reaction of benzaldehyde, pivalaldehyde, and furfural [2c–e,2g].

Comparing the results obtained with γ-alumina, KF/alumina, and KOH/alumina (entries 9–15 vs entries 16–19), it can be stated that the active sites on γ-alumina are much more appropriate for the present lactonization of **1** to **2** than those generated by supporting KF or KOH onto alumina.

Although hydrotalcite, La_2O_3, ZrO_2, and ZnO possess unique surface chemical properties and have been successfully applied to a number of organic catalytic reactions [1], they were all inactive for the present lactonization (entries 20–23). The low catalytic activities of these catalysts are not peculiar to the intramolecular Tishchenko reaction of **1** to **2**. The application of these catalysts to the intermolecular Tishchenko reaction of furfural and the mixed Tishchenko reaction of benzaldehyde and pivalaldehyde also resulted in failure [2e,2g].

Switching the solvent from benzene to relatively basic tetrahydrofuran retarded MgO- and γ-alumina-catalyzed reactions (entry 2 vs entry 3 and entry 13 vs entry 14), indicating that the oxygen atom of tetrahydrofuran and the carbonyl oxygen atom of **1** compete with each other for coordination onto acidic sites (metal cation) on MgO and γ-alumina. Thus, it can be stated that acidic sites (metal cation) on MgO and γ-alumina take part in the lactonization of **1** to **2**. Recently, Narske et al. also reported the similar inhibition effect of tetrahydrofuran solvent on the noncatalytic destructive adsorption of (2-chloroethyl)ethyl sulfide on nanocrystalline MgO [10].

3.2. Dependence of the catalytic activities of MgO and CaO in the intramolecular Tishchenko reaction of o-phthalaldehyde on pretreatment temperature of the catalysts

The surface chemical properties of alkaline earth oxides such as basicity and surface area are strongly affected by pretreatment temperature [1]. Thus, in general, the catalytic behaviors of alkaline earth oxides for various organic reactions vary with pretreatment temperature [1]. Fig. 1 shows the variations of the yield of **2** for MgO- and CaO-catalyzed intramolecular Tishchenko reaction of **1** to **2** as a function of pretreatment temperature when the reactions were carried out in benzene (1 mL) at 313 K for 1 h with 10 mg of catalyst and 1 mmol of **1**.

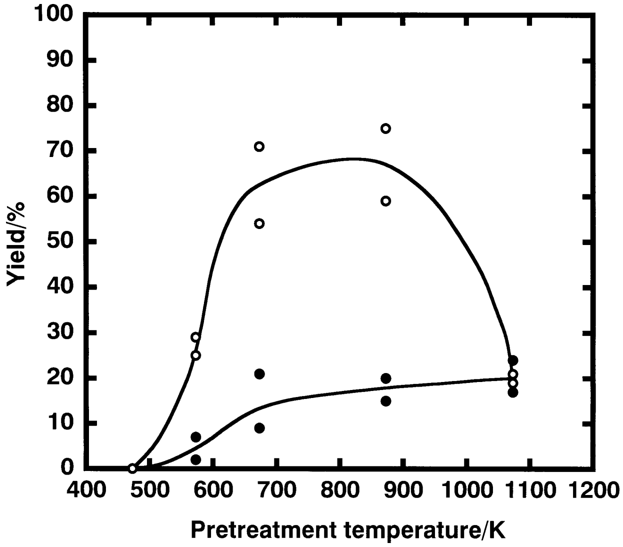


Fig. 1. Influence of evacuation temperature of $Mg(OH)_2$ (●) and $Ca(OH)_2$ (○) on the yield of phthalide (**2**). Reaction conditions were as follows: catalyst, 10 mg; *o*-phthalaldehyde (**1**), 1 mmol; benzene, 1 mL; reaction temperature, 313 K; reaction time, 1 h.

Both MgO and CaO showed no activities when they were pretreated at 473 K. For MgO and CaO to exhibit catalytic performance, pretreatment above 473 K is required, implying that the main active basic sites on MgO and CaO for the present lactonization are not OH groups but O^{2-} ions [1].

The activity of MgO increased with an increase in pretreatment temperature in the range from 473 to 1073 K, although the pretreatment above 873 K leads to a decrease in the surface basicity of MgO [1a]. The activity of CaO, on the other hand, increased as the pretreatment temperature rose up to 873 K, above which it decreased rapidly. The rapid decrease of the activity of CaO caused by the pretreatment above 873 K should be related to the decrease in the surface basicity and in the surface area (i.e., 48 m^2/g at 873 K; 32 m^2/g at 1073 K).

3.3. Dependence of the catalytic activity of γ-alumina (JRC-ALO-4) in the intramolecular Tishchenko reaction of o-phthalaldehyde on pretreatment temperature of the catalyst

On exposure to air at room temperature, the surface of γ-alumina is considered to be hydrated by the chemical and sometimes physical adsorption of water. In this state, γ-alumina usually provides poor catalytic activity, because the surface atoms are saturated by hydroxyl groups, each of which is directly above an aluminum ion in the next layer of the crystallite. However, when γ-alumina in such an inert state is treated at higher temperatures under high vacuum, dehydration takes place to yield another state of

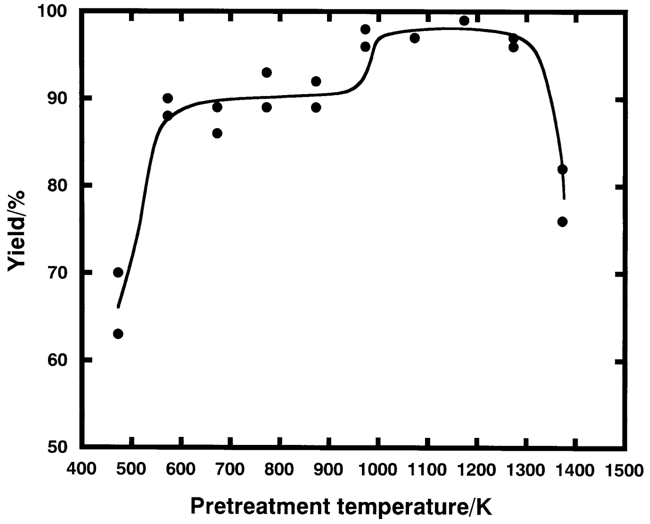


Fig. 2. Influence of evacuation temperature of γ-alumina on the yield of phthalide (**2**). Reaction conditions were as follows: catalyst, 50 mg; *o*-phthalaldehyde (**1**), 1 mmol; benzene, 1 mL; reaction temperature, 313 K; reaction time, 4 h.

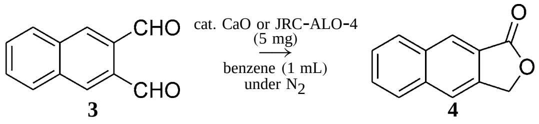
γ-alumina having highly unsaturated surface atoms [1a,9] some of which should act as catalytically active sites for the present lactonization of **1** to **2**.

Variation of the yield of **2** as a function of the pretreatment temperature of JRC-ALO-4 is shown in Fig. 2. All reactions were performed in benzene (1 mL) at 313 K for 4 h under N_2 with **1** (1 mmol) and JRC-ALO-4 (50 mg). The pretreatment in the temperature range from 973 to 1273 K resulted in almost quantitative conversion of **1** to **2**. The result that the pretreatment above 1273 K gave rise to a sharp decline in the activity should be related to the partial transformation of γ to α structure that is the most stable and thus the least reactive among aluminum oxides. The decrease in the surface area of JRC-ALO-4 (149 m^2/g at 1273 K; 101 m^2/g at 1373 K) also supports this conjecture. In the pretreatment temperature range from 573 to 873 K, JRC-AlO-4 exhibited nearly constant excellent activities. The activity shows a sharp fall when pretreated below 573 K. Since dehydration of JRC-ALO-4 is enhanced with an increase in pretreatment temperature [1a,9], the continuous increase in the activity in the pretreatment temperature range from 473 to 1273 K demonstrates that the active sites for the present lactonization are unsaturated Al^{3+} and O^{2-} ions on the surface. It is natural that the greater polarized surface environment should interact more efficiently with the polarized carbonyl group of **1** to yield **2**. It must be emphasized that JRC-ALO-4 exclusively furnished **2** at any pretreatment temperature.

3.4. Application of CaO and γ-alumina (JRC-ALO-4) to the intramolecular Tishchenko reaction of 2,3-naphthalenedicarbaldehyde

The heterogeneous catalytic systems realized by the use of CaO and γ-alumina pretreated at 873 and 773 K, respectively, in vacuo for 2 h were also successfully applicable to the selective intramolecular Tishchenko reaction of 2,3-naphthalenedicarbaldehyde (**3**) possessing greater conjugated system in comparison with **1**. Table 2 summarizes the results of the application of CaO and γ-alumina (JRC-ALO-4) to the intramolecular Tishchenko reaction of **3** to the corresponding lactone **4**. Treatment of **3** (0.1 mmol) with CaO (5 mg) for 2 h and JRC-ALO-4 (5 mg) for 20 h in benzene (1 mL) at 313 K led to relatively poor results; the corresponding five-membered lactone **4** was obtained in 21 and 74% yields, respectively (entries 1 and 3). However, raising the reaction temperature from 313 to 333 K further enhanced the yields of **4** to 94% and quantitative, respectively (entries 2 and 4). Just as the results obtained with **1**, CaO and γ-alumina furnished **4** selectively without producing any other by-product.

Table 2
Application of CaO and γ-alumina to the intramolecular Tishchenko reaction of 2,3-naphthalenedicarbaldehyde (**3**)



3
(0.1 mmol)

4

Entry	Catalyst	Pretreatment temperature (K)	Surface area[a] (m^2/g)	Reaction temperature (K)	Reaction time (h)	Yield[b] (%)
1	CaO	873	48	313	2	21
2	CaO	873	48	333	2	94
3	ALO-4	773	173	313	20	74
4	ALO-4	773	173	333	20	quant.

[a] Determined by BET method.

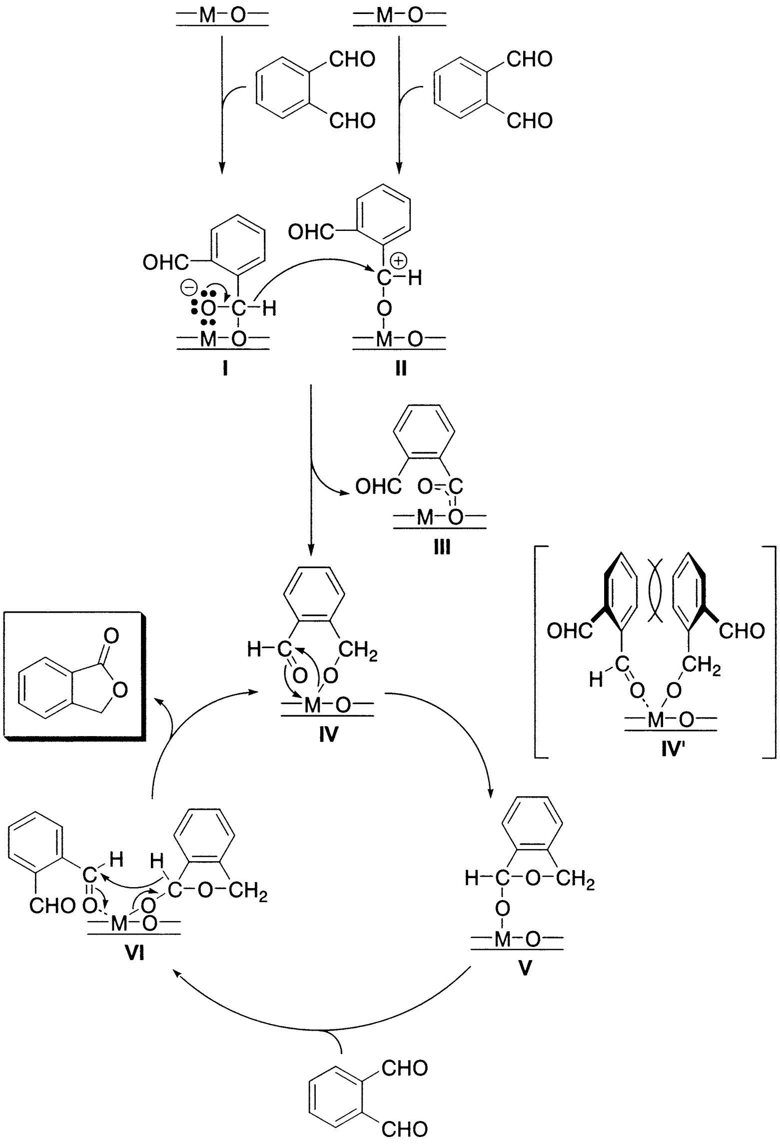
[b] Determined by GC equipped with a column of DB-1.

Bergens et al. reported that the lactonization of **3** to **4** was faster than that of **1** to **2** in the $[Rh(diphosphine)(acetone)_2]^+$-catalyzed reaction [5]. However, in CaO and γ-alumina catalytic systems, **3** was less reactive than **1**.

3.5. Mechanistic consideration

A plausible reaction mechanism of the intramolecular Tishchenko reaction of **1** to **2** over MgO is depicted in Scheme 2. The catalytic cycle in this proposed mechanism is essentially similar to the mechanism proposed for the classical Tishchenko reaction catalyzed by aluminum alkoxides [3f].

First, the dialdehyde **1** is adsorbed on the basic site (O^{2-}) or the acidic site (Mg^{2+}) to form intermediates **I** and **II**, respectively, then the hydride ion transfer from **I** to **II** takes place to provide **III** and intermediate **IV**. The existence of **III** and **IV** on the surface of MgO was confirmed by infrared spectroscopy. Fig. 3 shows the change in the infrared spectra of **1** adsorbed on MgO and Fig. 4 shows it adsorbed on γ-alumina (discussed later) with evacuation temperature. The absorption bands at 1753 and 1704 cm^{-1} that decreased remarkably when the evacuation temperature



Scheme 2. Proposed mechanism for the intramolecular Tishchenko reaction of *o*-phthalaldehyde (**1**) to phthalide (**2**) over MgO and γ-alumina. M and O represent an acidic site (metal cation) and a basic site (O^{2-}), respectively.

was raised from room temperature to 473, 573, and 673 K can be assigned to the vibrations of the C=O bond of the aldehyde group. The absorption band at 2704 cm^{-1} due to the stretching of the C–H bond of the aldehyde group also indicates the presence of the aldehyde group. The absorption bands at 1566 and 1400 cm^{-1} can be assigned to the asymmetric and symmetric stretching vibrations of the carbonate group of **III**, respectively. On the other hand, since the absorption bands due to the stretching of the CH_2 group of magnesium benzylate are considered to appear at 2940 and 2860 cm^{-1} [2a], it can be deduced that the absorption bands at 2960 and 2855 cm^{-1} can be assigned to the CH_2 group of **IV**. In the case of benzaldehyde adsorbed on MgO, the absorption bands due to the aldehyde group disappeared completely when evacuation was conducted above 453 K, because the adsorbed species such as magnesium benzylate and magnesium benzoate do not possess any aldehyde groups [2a]. However, in the case of **1** adsorbed on MgO, the absorption bands due to the aldehyde group do not disappear even at higher evacuation temperatures of 473, 573, and 673 K. This indicates that the chemically adsorbed species possessing the aldehyde group exist on the surface of MgO. Thus, together with the observed absorption bands due to the carbonate group of **III** and the CH_2 group of **IV**, it is conjectured that the adsorption of **1** on MgO results in the formation of **III** and **IV**. Although **III** remains on MgO as inert adsorbed species, **IV** becomes the active species for the catalytic formation of **2** as described below.

Tanabe and Saito reported that the addition of benzyl alcohol in the CaO-catalyzed Tishchenko reaction of benzaldehyde shortens the induction period remarkably, because of the rapid formation of calcium benzylate, $PhCH_2O$–Ca, via the abstraction of the proton from benzyl alcohol by basic sites (O^{2-}) on CaO [2a]. In addition, Ogata

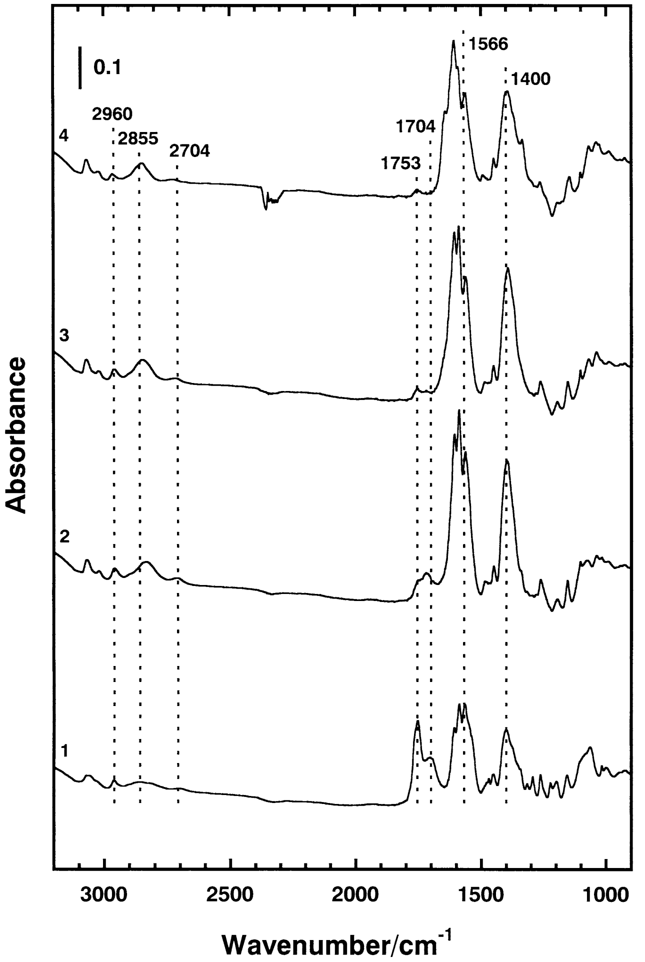


Fig. 3. Infrared spectra of *o*-phthalaldehyde (**1**) adsorbed at room temperature on MgO. Spectrum 1: evacuated at room temperature for 20 min. Spectrum 2: evacuated at 473 K for 20 min. Spectrum 3: evacuated at 573 K for 20 min. Spectrum 4: evacuated at 673 K for 20 min.

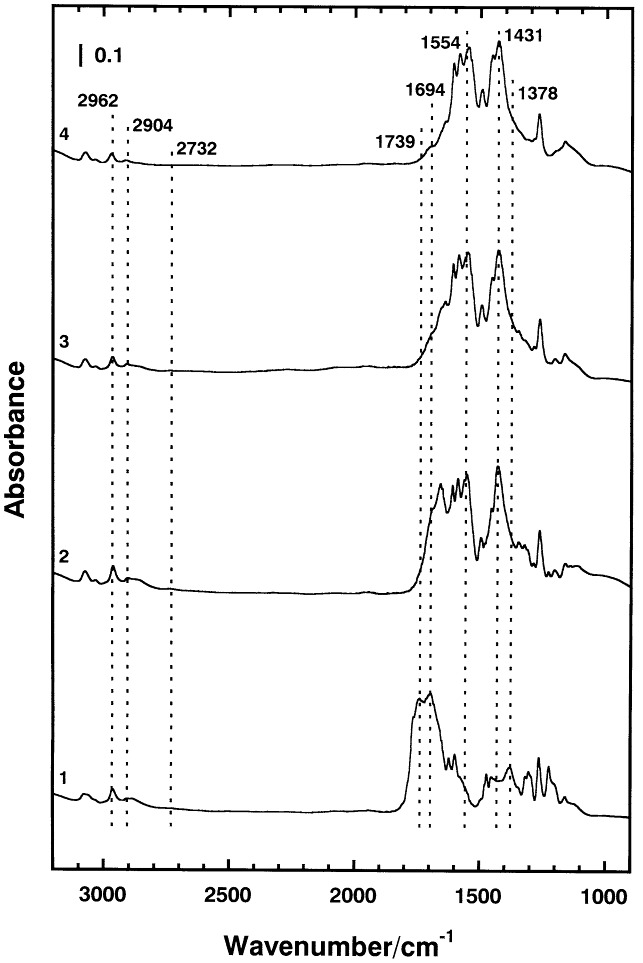


Fig. 4. Infrared spectra of *o*-phthalaldehyde (**1**) adsorbed at room temperature on γ-alumina. Spectrum 1: evacuated at room temperature for 20 min. Spectrum 2: evacuated at 473 K for 20 min. Spectrum 3: evacuated at 573 K for 20 min. Spectrum 4: evacuated at 673 K for 20 min.

and Kawasaki demonstrated for the aluminum alkoxide-catalyzed Tishchenko reaction that the alkoxide ion transfer from the catalyst to an aldehyde is an indispensable step for providing product esters [3f]. Thus, the alkoxide ion in **IV** without question participates in the present lactonization and is likely to attack the electrophilic carbonyl carbon atom of the aldehyde group existing in the same active species **IV** to yield the corresponding cyclic intermediate **V**. It is conjectured that **V** draws another dialdehyde **1** onto Mg^{2+}, followed by the hydride ion transfer via a six-membered transition state to furnish **IV** and the product lactone **2**.

To obtain much more information about the molecular and electronic structures of **1**, **3**, and the potential intermediates **IV** and **V**, we attempted quantum chemical calculations at the PM3-MO level of theory [8], where it was assumed that **IV** and **V** are adsorbed on the Mg atom on the first layer of the cluster model $(MgO)_{16}$. The charges on the carbonyl carbon and oxygen atoms for **1** and **3** are given in Table 3. The atomic charges, bond lengths, and bond angles of the adsorption states of **IV** and **V** shown in Figs. 5 and 6, respectively, are listed in Tables 4 and 5. Although **3** was less reactive than **1** in CaO- and γ-alumina-catalyzed intramolecular Tishchenko reactions, the charges on the carbonyl carbon and oxygen atoms that are relevant to adsorption onto the surface of CaO and γ-alumina are almost equal (Table 3). It should be noted that the carbonyl carbon atom of the active species **IV** is more positively charged than that of **1** (entry 1 in Table 3 vs entry 4 in Table 4), indicating that the carbonyl carbon atom in **IV** is more reactive for the nucleophilic addition of the alkoxide ion in **IV** than that in **1**. Concerning the intermediate **V**, the quantum chemical calculations suggest that the bidentate coordination onto two magnesium atoms is

Table 3
Charges on carbonyl carbon and oxygen atoms for *o*-phthalaldehyde (**1**) and 2,3-naphthalenedicarbaldehyde (**3**) calculated at the PM3-MO level of theory

Entry	Aldehyde	Atom	Charge
1	**1**	Carbonyl carbon	+0.312
2	**1**	Carbonyl oxygen	−0.303
3	**3**	Carbonyl carbon	+0.315
4	**3**	Carbonyl oxygen	−0.309

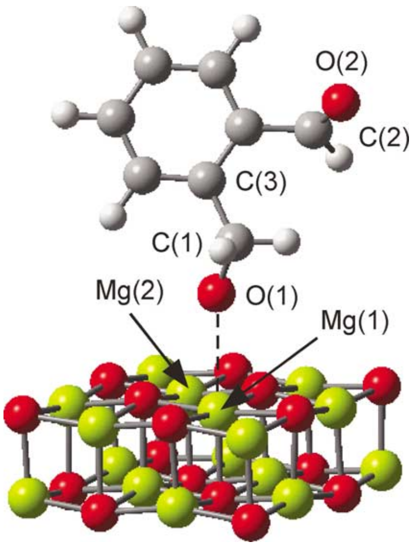


Fig. 5. Optimized structure of the intermediate **IV** calculated by PM3–MO method. Bond lengths and angles are in Å and degrees, respectively.

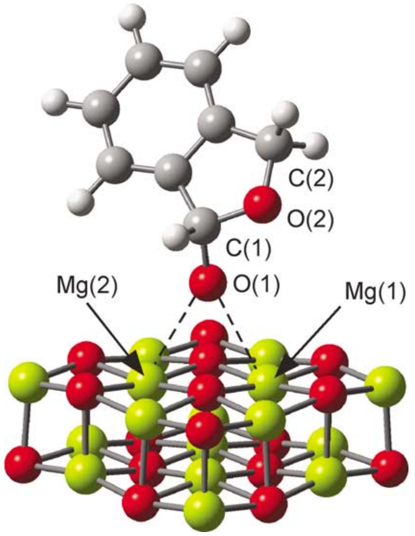


Fig. 6. Optimized structure of the intermediate **V** calculated by PM3–MO method. Bond lengths and angles are in Å and degrees, respectively.

more stable for the organic adsorbed species than the unidentate species (Fig. 6). This type of bidentate coordination enables another dialdehyde **1** to approach easily one of the two Mg atoms to form the corresponding intermediate **VI**, because the spaces above the two Mg atoms should be relatively vacant.

Based on the kinetic study, Tanabe and Saito suggested for the Tishchenko reaction of benzaldehyde over CaO that the rate-determining step in the catalytic cycle is the alkoxide ion transfer from surface calcium benzylate to the carbonyl carbon atom of benzaldehyde [2a]. We have also found that the selectivities to the four Tishchenko dimers formed in the mixed Tishchenko reaction over MgO and CaO are determined primarily in the step of the alkoxide ion transfer to an aldehyde [2g]. Thus, it is conjectured that the formation of **V** from **IV** is the rate- and/or selectivity-determining step in the catalytic cycle.

Table 4
Atomic charges in the intermediates **IV** and **V** calculated at the PM3-MO level of theory

Entry	Intermediate[a]	Atom	Charge
1	**IV**	Mg(1)	+0.582
2	**IV**	Mg(2)	+0.575
3	**IV**	C(1)	+0.122
4	**IV**	C(2)	+0.328
5	**IV**	O(1)	−0.141
6	**IV**	O(2)	−0.308
7	**V**	Mg(1)	+0.581
8	**V**	Mg(2)	+0.571
9	**V**	C(1)	+0.259
10	**V**	C(1)	+0.127
11	**V**	O(1)	−0.085
12	**V**	O(2)	−0.296

[a] The models of the intermediates **IV** and **V** used for the present calculations are shown in Figs. 5 and 6, respectively.

Table 5
Bond lengths and bond angles in the intermediates **IV** and **V** calculated at the PM3-MO level of theory

Entry	Intermediate[a]	Bond length (Å) and bond angle (degrees)	
		Bond length	
1	**IV**	Mg(1)–O(1)	2.630
2	**IV**	O(1)–C(1)	1.342
3	**V**	Mg(1)–O(1)	2.518
4	**V**	Mg(2)–O(1)	2.519
5	**V**	O(1)–C(1)	1.360
		Bond angle	
6	**IV**	Mg(1)–O(1)–C(1)	155.3
7	**IV**	O(1)–C(1)–C(3)	117.4
8	**V**	Mg(1)–O(1)–C(1)	153.7
9	**V**	Mg(2)–O(1)–C(1)	142.9
10	**V**	Mg(1)-O(1)-Mg(2)	65.8

[a] The models of the intermediates **IV** and **V** used for the present calculations are shown in Figs. 5 and 6, respectively.

The quantum chemical calculations imply that the oxygen atom of the alkoxide ion in **IV** is considerably hindered by the above aryl group (Fig. 5 and entries 1, 2, 6, and 7 in Table 5), indicating the difficulty of the formation of the sterically congested **IV**′. In addition, the quantum chemical calculations demonstrate that the carbonyl carbon atom of **IV** is more positively charged and thus more reactive for the nucleophilic addition of the alkoxide ion in the active species **IV** than that of **1** (entry 1 in Table 3 vs entry 4 in Table 4). Furthermore, the reaction between an alkoxide ion and an aldehyde group in the same active species **IV** to form the corresponding cyclic intermediate **V** without doubt involves smaller loss in entropy of activation than the same reaction between an alkoxide ion in **IV** and an aldehyde group in another dialdehyde **1** leading to the intermolecular Tishchenko product. Therefore, it can be concluded that the attractive result that MgO furnishes **2** exclusively without producing any intermolecular Tishchenko products should arise from the intramolecular alkoxide ion transfer in **IV** occurring rapidly and thus predominantly.

We also became interested in the reaction mechanism of the intramolecular Tishchenko reaction of **1** to **2** over γ-alumina and measured the infrared spectra of the adsorbed **1** on γ-alumina. The change in the infrared spectra of **1** adsorbed on γ-alumina (JRC-ALO-4) with evacuation temperature is shown in Fig. 4. The absorption bands at 1554 and 1431 cm^{-1} whose intensities increased remarkably when evacuation was conducted above 473 K can be assigned to the asymmetric and symmetric stretching vibrations of the carbonate group of **III**, respectively. The absorption bands at 2962 and 2904 cm^{-1} can be assigned to the stretching of the CH_2 group of **IV**. Kuiper et al. pointed out the possibility that the band at 1370 cm^{-1} which appears when benzyl alcohol is adsorbed on alumina is due to the vibration of the $–CH_2–O–$ group of aluminum benzylate [11]. Thus, the absorption band at 1378 cm^{-1}, which continued to diminish as the evacuation temperature was raised, may be due to the vibration of the $–CH_2–O–$ group of **IV**. In the case of benzaldehyde adsorbed on alumina, Kuiper et al. reported that the absorption band due to the vibration of the $C{=}O$ bond of the aldehyde group is reduced to a considerably small shoulder by evacuation at room temperature and disappears almost completely by evacuation at 503 K [11]. In the case of **1** adsorbed on γ-alumina, however, the strong absorption bands due to the vibrations of the carbonyl group were confirmed at 1739 and 1694 cm^{-1} when evacuation was performed at room temperature. In addition, even at higher evacuation temperatures of 473, 573, and 673 K, the bands due to the carbonyl group did not disappear, implying that chemically adsorbed species with an aldehyde group, namely **III** and **IV**, exist on the surface of γ-alumina. As for the stretching of the C–H bond of the aldehyde group, a very weak absorption band was confirmed at 2732 cm^{-1}. Since the formations of **III** and **IV** on γ-alumina were confirmed, it can be deduced that the lactonization of **1** to **2** over γ-alumina occurs by the same mechanism as that over MgO shown in Scheme 2.

Tanabe and Saito postulated that the reason that the Tishchenko reaction of benzaldehyde hardly proceeds over γ-alumina should be related to the fact that aluminum benzylate is easily oxidized to the corresponding surface carboxylate such as aluminum benzoate [2a]. The remarkable increase of the absorption bands due to the carbonate group and the remarkable decrease of the band due to the $–CH_2–O–$ group in **IV** when evacuation temperature was raised from room temperature to 473 K demonstrate that a higher temperature enhances such an oxidation. Knözinger et al. also reported that aluminum benzylate is easily oxidized at high temperatures, i.e., 433 and 443 K [12]. Presumably, the intramolecular alkoxide ion transfer in the active species **IV** producing the intermediate **V** takes place much faster than the oxidation of **IV** and the intermolecular alkoxide ion transfer from **IV** to another **1** at a low reaction temperature of 313 K, and thus the smooth and exclusive lactonization of **1** to **2** can be realized over γ-alumina at 313 K as listed in entries 9–15 in Table 1. The facility of the intramolecular alkoxide ion transfer in **IV** to yield **V** can be explained by the similar consideration described for the same reaction over MgO.

4. Conclusion

We have developed a new synthetic method for the synthesis of phthalide–skeleton under mild conditions using heterogeneous catalytic intramolecular Tishchenko reaction with environmentally benign, economical, and highly effective solid bases such as MgO, CaO, SrO, and γ-alumina. It should be noted that the intramolecular Tishchenko reactions of *o*-phthalaldehyde and 2,3-naphthalenedicarbaldehyde to the corresponding lactones over these metal oxides proceeded quite smoothly and selectively without producing any byproducts including the intermolecular Tishchenko products. The present approach is certainly one of the potential answers toward an increasing demand for the selective, nontoxic, and effective organic reactions providing phthalide–skeletons that are contained in a number of pharmaceuticals and naturally occurring compounds exhibiting significant biological activities and are employed in the synthetic precursors of more complex compounds.

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References

[1] (a) K. Tanabe, M. Misono, Y. Ono, H. Hattori, New Solid Acids and Bases, Kodansha–Elsevier, Tokyo–Amsterdam, Oxford, New York, Tokyo, 1989;
(b) H. Hattori, Chem. Rev. 95 (1995) 537;
(c) Y. Ono, T. Baba, Catal. Today 38 (1997) 321;
(d) H. Hattori, Appl. Catal. 222 (2001) 247.

[2] (a) K. Tanabe, K. Saito, J. Catal. 35 (1974) 247;
(b) H. Tsuji, F. Yagi, H. Hattori, H. Kita, J. Catal. 148 (1994) 759;
(c) H. Handa, T. Baba, H. Sugisawa, Y. Ono, J. Mol. Catal. 134 (1998) 171;
(d) H. Kabashima, H. Tsuji, S. Nakata, Y. Tanaka, H. Hattori, Appl. Catal. 194–195 (2000) 227;
(e) T. Seki, K. Akutsu, H. Hattori, Chem. Commun. 11 (2001) 1000;
(f) T. Seki, H. Hattori, Chem. Commun. 23 (2001) 2510;
(g) T. Seki, H. Kabashima, K. Akutsu, H. Tachikawa, H. Hattori, J. Catal. 204 (2001) 393.

[3] For the use of traditional aluminum alkoxides as catalysts, see
(a) W. Tischtschenko, Chem. Zentralbl. 77 (I) (1906) 1309;
(b) W.C. Child, H. Adkins, J. Am. Chem. Soc. 47 (1925) 798;
(c) F.J. Villani, F.F. Nord, J. Am. Chem. Soc. 69 (1947) 2605;
(d) L. Lin, A.R. Day, J. Am. Chem. Soc. 74 (1952) 5133;
(e) T. Saegusa, T. Ueshima, J. Org. Chem. 33 (1968) 3310;
(f) Y. Ogata, A. Kawasaki, Tetrahedron 25 (1969) 929.

[4] For the use of advanced catalysts, see
(a) P.R. Stapp, J. Org. Chem. 38 (1973) 1433;
(b) M. Yamashita, Y. Watanabe, T. Mitsudo, Y. Takegami, Bull. Chem. Soc. Jpn. 49 (1976) 3597;
(c) T. Ito, H. Horino, Y. Koshiro, A. Yamamoto, Bull. Chem. Soc. Jpn. 55 (1982) 504;
(d) M. Yamashita, T. Ohishi, Appl. Organomet. Chem. 7 (1993) 357;
(e) K. Morita, Y. Nishiyama, Y. Ishii, Organometallics 12 (1993) 3748;
(f) S. Onozawa, T. Sakakura, M. Tanaka, M. Shiro, Tetrahedron 52 (1996) 4291;
(g) T. Ooi, T. Miura, K. Takaya, K. Maruoka, Tetrahedron Lett. 40 (1999) 7695;
(h) M.R. Bürgstein, H. Berberich, P.W. Roesky, Chem. Eur. J. 7 (2001) 3078.

[5] S.H. Bergens, D.P. Fairlie, B. Bosnich, Organometallics 9 (1990) 566.

[6] For example, see
(a) Q. Dang, B.S. Brown, P.D. van Poelje, T.J. Colby, M.D. Erion, Bioorg. Med. Chem. Lett. 9 (1999) 1505;
(b) H. Matsuda, H. Shimoda, M. Yoshikawa, Bioorg. Med. Chem. 7 (1999) 1445;
(c) S. Mori, S. Takechi, S. Shimizu, S. Kida, H. Iwakura, M. Hajima, Tetrahedron Lett. 40 (1999) 1165;
(d) H. Watanabe, T. Furuuchi, T. Yamaguchi, T. Kitahara, Org. Lett. 1 (1999) 1079;
(e) R. Bentley, Chem. Rev. 100 (2000) 3801; [And references therein.]
(f) T. Matsumoto, H. Yamaguchi, M. Tanabe, Y. Yasui, K. Suzuki, Tetrahedron Lett. 41 (2000) 8393;
(g) F. Bellina, D. Ciucci, P. Vergamini, R. Rossi, Tetrahedron 56 (2000) 2533; [And references therein.]
(h) S. Hayat, M.I. A-u-Rahman, Choudhary, K.M. Khan, E. Bayer, Tetrahedron Lett. 42 (2001) 1647; [And references therein.]
(i) R. Mukhopadhyay, N.G. Kundu, Tetrahedron 57 (2001) 9475; [And references therein.]
(j) T. Kawasaki, S. Saito, Y. Yamamoto, J. Org. Chem. 67 (2002) 2653; [And references therein.]
(k) T.R. Kelly, D. Xu, G. Martínez, H. Wang, Org. Lett. 4 (2002) 1527.

[7] S. Miyata, T. Kumura, H. Hattori, K. Tanabe, Nippon Kagaku Zasshi 92 (1971) 514.

[8] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, Ab-initio MO calculation program; Gaussian 98, revision A.9; Gaussian, Inc., Pittsburgh, PA, 1998.

[9] For a review for organic reactions on alumina, see G.W. Kabalka, R.M. Pagni, Tetrahedron 53 (1997) 7999.

[10] R.M. Narske, K.J. Klabunde, S. Fultz, Langmuir 18 (2002) 4819.

[11] A.E.T. Kuiper, J. Medema, J.J.G.M. van Bokhoven, J. Catal. 29 (1973) 40.

[12] H. Knözinger, H. Bühl, E. Ress, J. Catal. 12 (1968) 121.