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Catalytic, high-speed Tishchenko reaction using (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum) as a powerful bidentate catalyst

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Abstract

Exceedingly high-speed Tishchenko reaction of various aldehydes can be realized by using a powerful, bidentate aluminum catalyst. This catalytic system is also applicable to the highly stereoselective intramolecular Tishchenko reduction of β-hydroxy ketones. © 1999 Elsevier Science Ltd. All rights reserved.

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The Tishchenko reaction involves the dimerization of aldehydes giving the corresponding esters by an oxidation–reduction sequence (A) under the influence of aluminum alkoxides as illustrated in Scheme 1.[1] In view of the low reactivity, however, several transition metal complexes have been elaborated with limited success.[2,3] Quite recently, lanthanide amides have been found to be highly effective for this purpose.[4] Despite the industrial importance of the Tishchenko reaction (e.g., a precursor of epoxy resins) one might hesitate to use certain toxic, costly transition metal catalysts in place of the traditional, non-toxic aluminum alkoxides. Accordingly, the increasing demand for environmentally-conscious chemical processes impelled us to explore a truly efficient, aluminum-based Tishchenko catalyst as an ideal metal species in this context. The essential point of this project is the achievement of highly reactive Tishchenko catalysts by the rational design of aluminum reagents. Here we wish to report a catalytic, high-speed Tishchenko reaction using (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum) (**1**) as a desirable catalyst based on our recently developed bidentate Lewis acid chemistry (Scheme 1).[5]

First, we examined the catalytic activity of bidentate **1** in the Tishchenko reaction of cyclohexanecarbaldehyde. Treatment of cyclohexanecarbaldehyde with 1 mol% of in situ generated bidentate aluminum alkoxide **1** in toluene at 21°C resulted in the rapid formation of the corresponding carboxylic ester in 98% isolated yield after purification by flash chromatography (entry 1 in Table 1). It should be particularly emphasized that the amount of the catalyst **1** can eventually be reduced to 0.2 mol% without loss of

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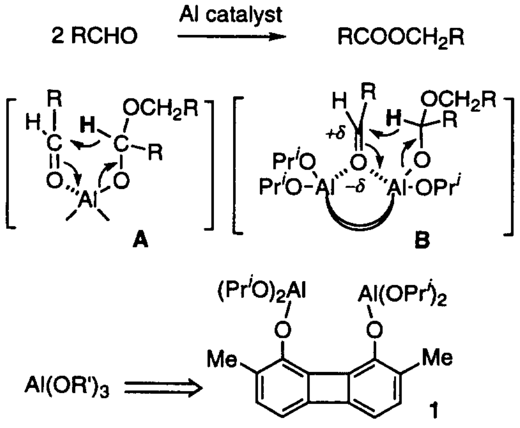


Scheme 1.

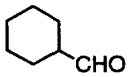
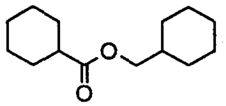
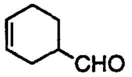
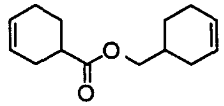
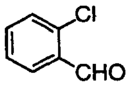
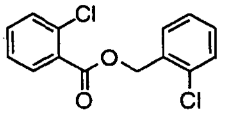
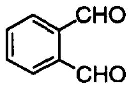
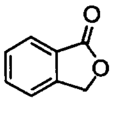
catalytic efficiency and the dimerization product was uniformly obtained in almost quantitative yield (entries 2–4 in Table 1). Therefore, the turnover frequencies (TOFs) of the present reaction should be more than 2000, even roughly estimated.[6] Notably, the dimerization of cyclohexanecarbaldehyde with the standard aluminum catalyst ($Al(OPr^i)_3$; 0.2 mol%) under otherwise similar reaction conditions gave only a trace amount of the ester, indicating the remarkable catalytic activity of the bidentate aluminum catalyst **1** based on the effective double electrophilic activation of carbonyl moiety as shown in (**B**) (Scheme 1).

As summarized in Table 1, a variety of aldehydes can be smoothly dimerized to carboxylic esters usually within 15 min, revealing the practicability of the present method. The potential of the aluminum based bidentate catalyst **1** was clearly demonstrated in the reaction of 3-cyclohexenecarbaldehyde and hexanal, and the corresponding Tishchenko products were constantly obtained in good to excellent isolated yields (entries 5–11). Although the catalytic system is effective for the dimerization of aromatic aldehydes, 1 mol% of the catalyst is generally required to attain a synthetically satisfactory level of reactivity and chemical yield (entries 12 and 13). *o*-Phthalaldehyde was found to be rapidly converted to the 5-membered lactone under relatively diluted conditions (entries 14 and 15).

Our approach has been successfully applied to the stereoselective intramolecular Tishchenko reduction of β-hydroxy ketones.[7] This transformation affords the corresponding *anti* diol monoesters in high yield with an excellent level of stereochemical control. For instance, initial treatment of β-hydroxy ketone **3** with (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**2**) (5 mol%) in toluene at 0~21°C for 30 min to ensure the in situ alkoxide formation and the subsequent reaction with benzaldehyde (R^1=Ph, 8 equiv.) at 21°C for 6 h gave rise to the corresponding *anti* diol monoester **4** (R^1=Ph) exclusively (*anti*:*syn*=>99:<1) in 99% yield. Hexanal ($R^1=C_5H_{11}$, 6 equiv.) was also found to be an effective hydride donor and the reaction proceeded to completion within 1 h, producing **4** ($R^1=C_5H_{11}$) in 92% yield (*anti*:*syn*=96:4) (Scheme 2).

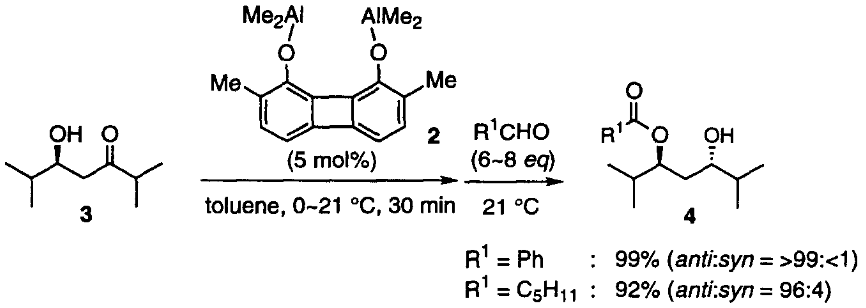
A typical experimental procedure is as follows (entry 2 in Table 1): 2,7-dimethyl-1,8-biphenylenediol (10.7 mg, 0.05 mmol) was placed in a dry two-neck flask with a stirring bar under Ar, and freshly distilled toluene (100 µL) was introduced.[9] To this suspension was added a 1 M hexane solution of Me_3Al (100 µL, 0.1 mmol) at 21°C and the solution was stirred for 30 min. Distilled isopropanol (15.3 µL, 0.2 mmol) was added and the stirring was continued for an additional 30 min. To the resulting solution was added freshly distilled cyclohexanecarbaldehyde (1.21 mL, 10 mmol) dropwise and the reaction mixture was stirred for 15 min at 21°C. The reaction was quenched by the addition of 1N HCl and the extractive

Table 1
High-speed Tishchenko reaction with bidentate aluminum catalyst **1**[a]

entry	aldehyde	mol % of catalyst **1**	condition (°C, h)	product	% yield[b,c]
1		1	21, 0.2		98
2		0.5	21, 0.25		99
3		0.3	21, 0.25		98
4		0.2	21, 0.25		98
5		1	21, 0.2		98
6		0.5	21, 0.25		99
7		0.3	21, 0.25		86
8	$CH_3(CH_2)_4CHO$	1	21, 0.2	$CH_3(CH_2)_4CO_2(CH_2)_5CH_3$	93
9		0.5	21, 0.25		92
10		0.3	21, 0.25		86
11		0.2	21, 0.25		75
12	PhCHO	1	21, 5	$PhCO_2CH_2Ph$	67 (76)[d]
13		1	21, 5		88
14		1	21, 0.25		83[e]
15		0.5	21, 0.25		70[e]

[a] The Tishchenko reaction of aldehydes was carried out in the presence of bidentate aluminum catalyst **1** in freshly distilled toluene under the given reaction conditions. [b] Isolated yield. [c] Substrate concentration of the reaction: 25 M (entries 1, 5, 8, 12, and 13); 50 M (entries 2, 6, and 9); 84 M (entries 3, 7, and 10); 125 M (entries 4 and 11). [d] Use of (2,7-dimethyl-1,8-biphenylenedioxy)bis(dibenzyloxyaluminum) as a catalyst.[8] [e] The reaction was performed in a concentration of 5 M because of low solubility of *o*-phthalaldehyde in toluene.

workup was performed with ether. The ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc:hexane=1:20 as eluent) gave the corresponding carboxylic ester as a colorless oil (1.11 g, 4.95 mmol; 99%).



Scheme 2.

Acknowledgements

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