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Catalytic Meerwein–Pondorf–Verley Reduction by Simple Aluminum Complexes

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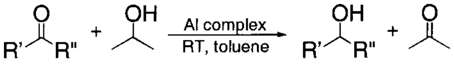
ABSTRACT



Catalytic MPV reduction was successfully carried out using simple aluminum precatalysts. Alkylaluminum reagents were converted to a low-aggregation aluminum alkoxide that was highly active for the MPV reduction of several carbonyl substrates in high yield (50–99%) using ^{i}PrOH as the reducing agent. A high degree of cis/trans selectivity was achieved in the reduction of 2-methylcyclohexanone (cis/trans = 20/80) by ^{i}PrOH. When chiral hydride sources were utilized in the reduction of 2-chloroacetophenone, high enantioselectivity (68–80% ee) was observed.

The Meerwein−Pondorf−Verley (MPV) reduction of carbonyl substrates to primary and secondary alcohols was first reported over 70 years ago.[1−3] The classical MPV reduction involves equilibrium-driven, reversible hydride transfer from a secondary alcohol, generally 2-propanol, to a carbonyl substrate activated through coordination to a Lewis acidic aluminum center.[4] A ketone byproduct, acetone, is formed as a volatile side product, and is easily removed. Although the MPV reduction has many practical advantages, such as being very chemoselective under mild reaction conditions and readily adaptable for both laboratory and large-scale synthesis, it has not found widespread utility in synthetic organic chemistry.[4] This is largely due to the fact that more than stoichiometric amounts of aluminum alkoxides are often required to obtain satisfactory yields of the alcohol in reasonable time.[4] Therefore, a method for the catalytic MPV reduction of organic carbonyls using simple aluminum complexes is highly desirable.

Since the initial discovery of the MPV reduction, there have been only a few reports in which aluminum alkoxides are used in catalytic amounts. These examples can be divided into two classes: (1) aluminum alkoxides that are "activated" by protic acids[5−8] and (2) "well-defined" aluminum reagents where the aluminum centers are complexed by multidentate ligands.[9−12] Rathke's $Al(O^iPr)_3$/acid cocatalyst system demonstrated good catalytic activity for the reduction of cyclohexanone to cyclohexanol.[8] However, this reaction is accompanied by significant amounts of side product formation, especially when enolizable substrates are used. The second class of catalyst is applicable to numerous aldehydes and ketones. Several research groups have shown that a variety of sophisticated aluminum complexes coordinated to multidentate ligands initiate catalytic MPV reduction in good yields and also demonstrate highly stereoselective hydride transfers when bulky, specialized ligands and/or chiral hydride sources are used.[10,11]

In our search for a catalytic asymmetric MPV reduction employing a chiral aluminum catalyst and 2-propanol, we discovered that simple alkylaluminum reagents are highly

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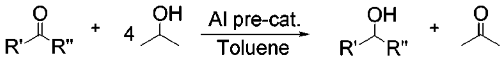
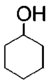
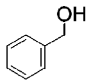
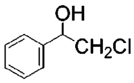
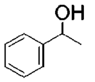
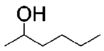
active catalyst precursors for the reduction of ketones and aldehydes in nonpolar organic solvents in the presence of excess 2-propanol. The resulting in situ generated, simple aluminum catalysts show higher activities than those of previously reported complex aluminum systems.[10,11] In addition, they demonstrate the same high level of stereoselectivity for hydride transfer that has been attributed solely to the elaborate ligand frameworks of reported catalysts. Herein, we report a remarkably efficient catalytic MPV reduction of carbonyl substrates using simple alkylaluminum pre-catalysts. Our results suggest that the efficiency and the selectivity of the Al-catalyzed MPV reaction does not depend on the presence of elaborate ligands. Rather, they are strongly affected by the aggregation state of the aluminum catalyst.

Classical MPV reduction of carbonyl substrates typically proceeds quite reluctantly. For example, reduction of cyclohexanone in toluene with Al(O^{i}Pr)$_3$ (10 mol %) and ^{i}PrOH (4 equiv) at room temperature gave cyclohexanol in only 7% yield after 12 h (Table 1, entry 1d). Under similar conditions, other ketone and aldehyde substrates (acetophenone, benzaldehyde, and 2-pentanone) were similarly unreactive (Table 1, entries 2d, 4d, and 5d). Contrastingly, the use of simple alkyl aluminum reagents (dimethylaluminum chloride or trimethylaluminum) as pre-catalysts with ^{i}PrOH (4 equiv) at room temperature produced primary and secondary alcohols in good yields within 2−12 h (Table 1, entries 1a,b−5a,b). The yield could also be increased by slightly elevating the reaction temperature (Table 1, entry 4a′).

Table 1. Catalytic MPV Reduction Using Simple Alkylaluminum Reagents



entry	product	Al pre-catalyst (10 mol%)	yield(%)	time(h)
1		a AlMe$_3$	82	3
		b AlMe$_2$Cl	96	2
		c AlMeCl$_2$	5	12
		d Al(O^{i}Pr)$_3$	7	12
2		a AlMe$_3$	91	2
		b AlMe$_2$Cl	60	1
		b′ AlMe$_2$Cl (neat ^{i}PrOH)	85	4
		c AlMeCl$_2$	6	12
		d Al(O^{i}Pr)$_3$	3	12
3		a AlMe$_3$	99	12
		b AlMe$_2$Cl	65	12
4		a AlMe$_3$	51	12
		a′ AlMe$_3$ (65 °C)	80	12
		b AlMe$_2$Cl	55	12
		d Al(O^{i}Pr)$_3$	0	12
5		a AlMe$_3$	11	12
		b AlMe$_2$Cl	50	12
		d Al(O^{i}Pr)$_3$	0	12

[a] Reaction conditions: Al pre-catalyst in 21 μM concentration, rt, N_2.

The results of Table 1 indicate for the first time that catalytic MPV reduction of organic carbonyls can be accomplished efficiently using a catalytic amount of a simple aluminum alkyl precursor. Titration studies in C_6D_6 using ^{1}H NMR spectroscopy have shown that AlMe$_3$ is completely converted to Al(O^{i}Pr)$_3$ under similar conditions (rt, 2 h, AlMe$_3$ at 25 μM concentration and 10 equiv of ^{i}PrOH). However, as shown in Table 1, commercial Al(O^{i}Pr)$_3$ shows very little catalytic activity under the same conditions. The main difference between the two Al alkoxides is that our in situ generated Al(O^{i}Pr)$_3$ is completely soluble in nonpolar organic solvents while the commercial Al(O^{i}Pr)$_3$ is not, presumably due to a higher degree of aggregation. The solubility of our in situ generated Al(O^{i}Pr)$_3$ suggests that it exists in a lower state of aggregation than commercial Al(O^{i}Pr)$_3$ (vide infra).

Barron, Interrante, and co-workers have reported that dimethylaluminum alkoxides formed in solution from trimethylaluminum and alcohols exist at equilibrium as a mixture of monomer, dimer, and trimer.[13,14] Several other groups have described the time-dependent changes in the physical properties of aluminum alkoxides, including an increase in the melting point of solid aluminum tris(alkoxide) over time.[15,16] This was attributed to an increase in aggregation of the aluminum complexes through bridging alkoxide ligands. It has been postulated that only nonbridging alkoxy groups are able to transfer hydrides to the carbonyl substrates.[8] Therefore, highly aggregated aluminum alkoxides would be detrimental to MPV reduction. On the basis of this, we attribute the remarkable efficiency of our catalytic MPV reduction to a low aggregation state of the aluminum catalyst where very few bridging alkoxides are present. The catalyst can be maintained in a low aggregation state in dilute solution for an extensive period. In fact, aging the trimethylaluminum/^{i}PrOH catalyst mixture for 6 days before the addition of cyclohexanone gave only a 20% decrease in the overall yield.

Interestingly, the presence of a chloride ligand diminishes the activity of AlMe$_2$Cl for the MPV reduction of benzaldehyde (Table 1, entry 2b). After the first hour, the reaction reaches a maximum yield of only 60% benzyl alcohol. However, the reaction can be carried to completion in neat ^{i}PrOH (Table 1, entry 2b′).

For aromatic aldehyde and ketone substrates, the AlMe$_2$Cl precatalyst tends to be less active than AlMe$_3$ (Table 1, entries 2a,b and 3a,b). However, AlMe$_2$Cl demonstrates significantly better activity than AlMe$_3$ toward the reduction of electron-rich ketones such as 2-pentanone (Table 1, entries 5a,b). Thermodynamically, 2-pentanone is a difficult substrate for MPV reduction.[4,17] The enhanced activity of AlMe$_2$Cl toward this substrate can be attributed to the increased Lewis acidity[18] of the aluminum center in

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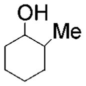
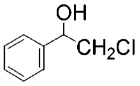
Table 2. Stereoselective MPV Reduction and Effect of Ligand Additives

product	entry	Al Reagent (10 mol%)	ligand	hydride source (equiv)	product selectivity	
					cis/trans	ee(%)[d]
	1[b]	$AlMe_2Cl$	5,10,15,20-tetraphenyl porphyrin	^{i}PrOH(4)	20/80	---
	2[a]	$AlMe_2Cl$	----	^{i}PrOH(4)	20/80	---
	3[c]	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol	*enantiopure*-α-methyl-2-napthyl methanol(1)	----	70
	4[a]	$AlMe_3$	----	*enantiopure*-α-methyl-2-napthyl methanol(1)	----	68
	5[c]	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol	*enantiopure-sec-o*-bromophenethyl alcohol(1)	----	82
	6[a]	$AlMe_3$	----	*enantiopure-sec-o*-bromophenethyl alcohol(1)	----	86-81[e]

[a] Reaction conditions: toluene (1 mL), 1,2,4,5-tetramethylbenzene (internal standard), N_2, Al reagent (21 μmol, 10 mol %), substrate (10 equiv), either chiral hydride source (1 equiv, 0 °C) or ^{i}PrOH (4 equiv, rt). [b] Reference 10 reports a cis/trans ratio of 8/92. Al(TPP)Cl under our reaction conditions (rt) yields a cis/trans ratio of 20/80. [c] Taken from ref 11; reactions carried out at 0 °C. [d] The absolute configuration of the major enantiomer of the product is opposite that of the chiral hydride source. [e] As would be expected for a reversible reaction, the enantioselectivity of the product decreases slowly over time.

$Al(OR)_2Cl$[19] which may lead to better coordination with electron-rich ketones[20] and thus give better activity for 2-pentanone.

Building upon the initial success found with our in situ generated catalyst, we sought to further investigate the stereoselective hydride transfer of this catalytic system (Table 2). Aluminum porphyrins have been found to exhibit high degrees of diastereoselectivity in the reduction of 2-methylcyclohexanone.[10] In addition, high degrees of catalyst activity and enantioselectivity in the reduction of α-chloroacetophenone with chiral hydride sources have been attributed to the use of linked bis(phenoxide) ligands.[11,10] As catalysts for the reduction of carbonyl compounds with a 2° alcohol, our simple alkylaluminum systems were found to be similar or superior in both catalytic activity and stereoselectivity to the aforementioned aluminum catalyst systems where elaborate ligands were employed. For example, the use of $AlMe_2Cl$ precatalyst yields a 20/80 cis/trans mixture of 2-methylcyclohexanol independent of the presence of *meso*-tetraphenylporphyrin (Table 2, entries 1−2). Similarly, using chirally pure 2° alcohols as the hydride source, $AlMe_3$ alone yields alcohol products with ee's that are comparable to those obtained in the presence of elaborate ligands (Table 2, entries 3−6).[11] Thus, our results show that the presence of ligands *is not necessary for either catalyst activity or stereoselective hydride transfer from chiral 2° alcohol* in the MPV reduction catalyzed by aluminum alkoxides.

In summary, we have observed for the first time an active and selective MPV catalyst system derived from simple alkylaluminum complexes. Our catalyst gives superior yields and reaction rates compared to those of other known aluminum-based catalysts. High diastereoselectivity was achieved in the reduction of 2-methylcyclohexanone in the absence of a ligand. High enantioselectivity in this reaction could also be achieved by using chiral alcohols as hydride sources. The realization that catalytic MPV reduction can be affected with simple alkylaluminum catalysts is significant and will lead to further developments in this area.

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Supporting Information Available: Experimental procedure, quantitative analysis (including typical GC traces), and ^{1}H NMR titrations. This material is available free of charge via the Internet at http://pubs.acs.org.

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