The Asymmetric Meerwein – Schmidt – Ponndorf – Verley Reduction of Prochiral Ketones with *i*PrOH Catalyzed by Al Catalysts**

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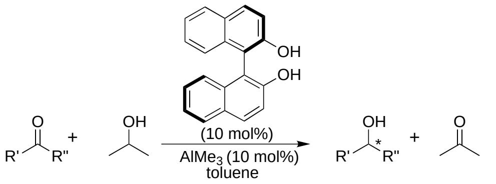
The Meerwein – Schmidt – Ponndorf – Verley (MSPV) reduction of carbonyl substrates to alcohols was first reported over seventy years ago.[1–3] It is highly chemoselective and utilizes *i*PrOH, an inexpensive hydride source.[4] However, since the late 1950s, the classical protocol for this reduction, where $Al(OiPr)_3$ was used as a reagent, has been largely replaced by methods using boro- and aluminum hydrides.[5, 6] This decrease in the application of the classical MSPV reduction is partly because greater than stoichiometric amounts of $Al(OiPr)_3$ are required to obtain satisfactory yields of the alcohol in a reasonable time.[4] Recently, we demonstrated that the catalytic behavior of the MSPV reduction is highly dependent upon the aggregation state of the aluminum complex and if freshly made, low-aggregate aluminum alkoxides are used as catalysts, high yields of the alcohol can be achieved under mild reaction conditions.[7]

The asymmetric MSPV-type reduction has long been prominent in synthetic methodology[8, 9] and the Evans[10] and Noyori[11] groups have further improved its utility by demonstrating the stereoselective reduction of prochiral ketones using chiral variants of this reaction. These reaction variants utilize an achiral hydride source, *i*PrOH; however, they employ chiral transition metal catalysts.[10, 11] To date, the only examples of asymmetric MSPV reduction using aluminum-based catalysts require the use of stoichiometric amounts of chiral alcohols as the hydride source.[7, 12, 13] Herein, we report a practical, enantioselective, catalytic MSPV reduction that utilizes *i*PrOH as the hydride source and is catalyzed by $AlMe_3$ and enantiopure 2,2'-dihydroxy-1,1'-biphenyl [BINOL; see Eq. (1)].

On the basis of earlier precedents in aluminum aryloxide chemistry,[14–16] we decided to combine (*R*)-(+)-BINOL and $AlMe_3$ in a 1:1 ratio in toluene, and observed a white precipitate after five minutes. With the addition of a prochiral ketone (10-fold excess) and *i*PrOH (40-fold excess), the reaction medium became homogeneous [Eq. (1)]. This simple method was found to effect the catalytic reduction of 2-chloroacetophenone at room temperature to give (*R*)-α-chloromethylbenzyl alcohol in 80% *ee* and 99% yield [see Eq. (2); Table 1, entry 1]. Similarly, using (*S*)-(−)-BINOL as the ligand produced the (*S*)-isomer (80% *ee*, 99% yield). The enantioselective reduction of 2-bromoacetophenone also proceeds smoothly (Table 1, entry 2). The reduction of the more electron-rich substrate propiophenone can also be achieved in high yield (80%) and moderate *ee* value (46%) by the addition of excess *i*PrOH (15-fold) (Table 1, entry 3).



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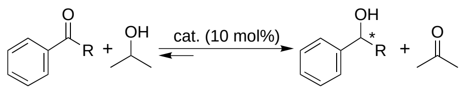

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Table 1. Asymmetric MSPV reduction.[a]

Entry	R	2-Propanol	Product	
		(equivalents[b])	Yield [%]	*ee* [%]
1	CH_2Cl	4	99	80 (*R*)[c]
		4	99	80 (*S*)[d]
2	CH_2Br	4	99	83 (*S*)[d]
3	CH_2CH_3	4	30	50 (*R*)[c]
		15	80	46 (*R*)[c]
4	$CH_2CH(CH_3)_2$	4	32	53 (*S*)[d]
		15	35	35 (*S*)[d]
5	$CH(CH_3)_2$	4	20	61 (*S*)[d]
		15	46	50 (*S*)[d]
6	CH_3	4	54	30 (*R*)[c]
		4	58	28 (*S*)[d]
		15	80	25 (*R*)[c]
7	CH_2OCH_3	4	95	8 (*R*)[c]
8	acetonaphthone[e]	4	41	48 (*S*)[d]
		15	43	46 (*S*)[d]

[a] Reaction conditions: BINOL (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μL); room temperature, N_2 for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reaction with (*S*)-(−)-BINOL. [e] acetonaphthone is the whole reactant, not an R group (not shown in Eq. (2)).

In general, substrates that are more sterically hindered than propiophenone lead to lower yields of the product (Table 1, entries 4 and 5), while a substrate that is less hindered gives a better yield but a lower *ee* value (Table 1, entry 6). As in the case of propiophenone (see above), a higher yield of the products can be obtained with increased *i*PrOH loading. Although α-methoxyacetophenone gives an excellent yield of the desired alcohol, the enantioselectivity is drastically reduced (Table 1, entry 7), probably because of the disruption of the tetradentate chiral intermediate (caused by the extra coordination of the MeO group, see below). Acetonaphthone (see Table 1, entry 8), which possesses a larger aromatic group than acetophenone, leads to higher enantioselectivity (Table 1, entry 8).

Given that the *ee* value was greatly increased by the presence of electron-withdrawing groups on the α-carbon of

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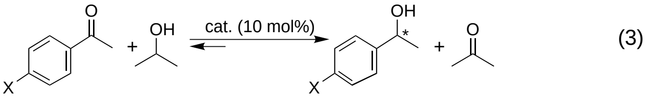
the acetophenone moiety, we decided to investigate the effect of inductive electronic parameters on the reaction shown in Equation (1). As expected, decreased electron density on the aromatic ring increases the yield of the desired alcohol.[17, 18] However, no significant change in *ee* value was observed (Table 2).

Table 2. Electronic effect on the MSPV reduction.[a]



(3)

Entry	X	2-Propanol (equivalents[b])	Product Yield [%]	Product *ee* [%]
1	H	4	54	30 (*R*)[c]
		15	80	25 (*R*)[c]
2	CH_3	4	44	30 (*R*)[c]
		15	62	20 (*S*)[d]
3	F	4	55	30 (*R*)[c]
		15	55	30 (*R*)[c]
4	Cl	4	70	30 (*R*)[c]
5	Br	4	70	30 (*R*)[c]

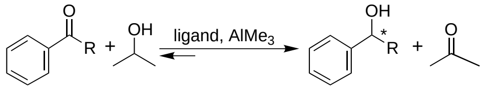
[a] Reaction conditions: BINOL (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μL); room temperature, N_2 for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reactions with (*S*)-(−)-BINOL.

A critical characteristic of the MSPV reduction system in Equation (1) is the favorable equilibrium (both synthetically and enantioselectively) exhibited by the BINOL–Al catalyst for the monoaromatic ketone and *i*PrOH reagent pairs. Unlike previous aluminum-based asymmetric MSPV reductions, which utilized aromatic chiral alcohols as their hydride sources,[7, 12] the enantiomeric purity of our product is maintained even after prolonged exposure to the catalyst system (see Supporting Information). After 24 h under catalytic equilibrium conditions (10 mol% (*R*)-BINOL, based on $AlMe_3$, 20 equivalents *i*PrOH, 20 equivalents acetone), the enantiomeric excess of a sample of chirally pure (*R*)-1-phenylethanol (98% *ee*) only decreased to 93%.

The results in Tables 1 and 2 are exciting because they indicate, for the first time, that catalytic, asymmetric MSPV reduction of prochiral ketones can be accomplished using simple aluminum-based catalysts and an achiral hydride source. We were curious about the role of BINOL in this reaction and set out to investigate the effect of the ligand concentration and ligand binding mode, by exploring aluminum complexes of ligands **1**–**3** (Scheme 1).

The addition of excess BINOL to the reaction in Equation (1), in which the substrate is acetophenone, does not affect the *ee* value but is detrimental to the product yield. A 1.5:1 ratio of BINOL:$AlMe_3$ decreases the product yield by half and a 2:1 ratio of BINOL:$AlMe_3$ prevents the reaction completely. The use of ligand **3** produces a very low yield of the desired alcohol (Table 3). Other primary amines, such as 2-aminopyridine and 1-(1-naphthyl)ethylamine, were also found to prevent the reaction completely. In comparison to BINOL, ligand **1** maintains the same product yield, however there is a marked decrease in the *ee* value (Table 3). Increasing the **1**:$AlMe_3$ ratio to 2:1 diminishes the yield of the product but does not further affect the *ee* value of the reaction. Interestingly however, with the neutral ligand **2**, which can not deprotonate before coordination to the aluminum catalyst, the yield and *ee* value of the product are significantly diminished, compared to 1 equivalent of BINOL.

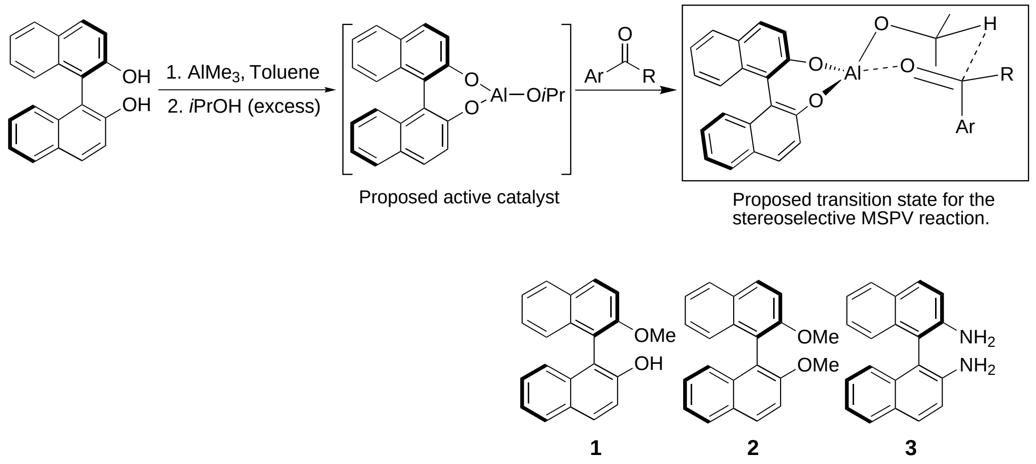
Table 3. Effect of ligand additive on the MSPV reduction.[a]



(4)

R = Me				R = CH_2Cl			
Ligand	Ligand:$AlMe_3$	Yield [%]	*ee* [%]	Ligand	Ligand:$AlMe_3$	Yield [%]	*ee* [%]
BINOL	1:1	54	30	BINOL	1:1	99	80
BINOL	2:1	0	–	BINOL	2:1	0	–
1	1:1	58	0	**1**	1:1	99	15
1	2:1	40	0	**1**	2:1	90	12
1	4:1	20	0	**1**	4:1	60	0
2	1:1	25	0	**2**	1:1	90	10
3	1:1	7	0	**3**	1:1	25	0

[a] Reaction conditions: ligand **1**–**3** (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), *i*PrOH (0.80 mmol), and toluene (500 μL); room temperature, N_2 for 16 h.



Scheme 1. Proposed active catalyst and transition state for the stereoselective MSPV reaction catalyzed by [(binol)Al(O*i*Pr)]. Ligands **1**, **2**, and **3** do not allow for an optimal MSPV geometry (a tetrahedral, four coordinate transition state) around the aluminum center.

We reported that tetradentate ligands hinder hydride transfer by aluminum catalysts.[7] In the classical MSPV reduction, the aluminum center is believed to be tetracoordinate during the hydride transfer from one of the isopropoxide ligands to the coordinated ketone substrate.[4] We believe that maximum *ee* value is achieved in our system when two of the aluminum alkyl groups of $AlMe_3$ are protonated by both phenolic protons, to form a 1:1 metal:BINOL complex during the initial catalyst formation stage. The third aluminum alkyl bond is then protonated by *i*PrOH. We believe this monomeric [(binol)(*i*PrO)Al] complex (Scheme 1) is the active chiral catalyst for this asymmetric reduction. Indeed, the use of an isolated sample of [(binol)AlMe(thf)], the THF-solvated precursor of [(binol)(*i*PrO)Al], leads to similar catalytic activity and selectivity in the reduction of α-bromoacetophenone (95% yield and 79% *ee*; see Table 1, entry 2; see Supporting Information).

A preferred requirement for the aforementioned model is that the active catalyst center is tetrahedral during the hydride transfer. Accounting for the necessary $i\mathrm{PrO}^-$ ion and the carbonyl substrate, this model leaves only two open coordination sites for any ligand to occupy. We believe that any catalytic system in which the ligands coordinate to the metal center so as to occupy more than two coordination sites will reduce the reaction rate. The diminished activity observed when excess bidentate ligand is used (see above) supports this theory.

Increased loading of *i*PrOH shifts the equilibrium to a higher yield for the desired product, but also decreases the *ee* value (Tables 1, entries 3–6). This effect may be explained by a decrease in the effective bidentate coordination of BINOL by competing *i*PrOH coordination, thereby decreasing the *ee* value. This is a minimal factor, however, because changing from four to over 15 equivalents of *i*PrOH decreased the *ee* value at most by 5–15%, while increasing the yield by over 50% for propiophenone (Table 1, entry 3).

In summary, we have observed for the first time an asymmetric MSPV reduction that utilizes an achiral hydride source and a chiral aluminum alkoxide catalyst. A high yield was achieved using a variety of ketone substrates and a good *ee* value was obtained when the carbonyl α-carbon was sufficiently electron withdrawing.

Experimental Section

Available in the Supporting Information: General experimental procedure, quantitative analysis (including chiral gas chromatography (GC) traces), plots of conversion and *ee* value versus time for the reduction of α-bromoacetophenone, and the characterization of the proposed active chiral aluminum alkoxide catalyst (9 pages).

General MSPV Reduction Procedure: All reactions were carried out under a dry nitrogen atmosphere unless otherwise noted. Toluene (500 µL) and enantiopure BINOL (5.8 mg, 0.02 mmol) were added to a 4-mL vial, equipped with a magnetic stirrer bar. $AlMe_3$ (1.9 µL, 0.02 mmol) was added to the mixture by syringe and the reaction was stirred for 5 min, after which time a white precipitate had formed. The carbonyl substrate (10 equiv.) and 2-propanol (40 or 150 equiv.) were added, and the vial was sealed with a teflon-lined silicone septum. The reaction was stirred at room temperature under nitrogen for 16 h. Aliquots (20 µL) were passed through a plug of neutral aluminum oxide (activated, Brockmann activity 1, ~150 mesh) and analyzed by GC to determine selectivity and conversion data (see the Supporting Information).

Scale-up Asymmetric MSPV Reduction: In the drybox, toluene (2 mL) was added to a 20-mL vial, equipped with a magnetic stirrer bar, and containing (*S*)-(−)-BINOL (57.3 mg, 0.2 mmol). $AlMe_3$ (19.7 µL, 0.2 mmol) was added to the mixture by syringe and the reaction was stirred for 5 min, after which time a white precipitate had formed. α-Bromoacetophenone (0.40 g, 2.0 mmol) and 2-propanol (610 µL, 8.0 mmol) were added and the vial was sealed with a teflon-lined cap, taken out of the drybox, and stirred at room temperature under nitrogen for 16 h. Flash column chromatography using 230–400 mesh silica gel (Merck, column dimensions = 2.5 cm × 12 cm) and CH_2Cl_2 as eluent gave a pure sample of α-(bromomethyl)benzyl alcohol, in 93% yield and 79% *ee*.

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