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Aluminum-based catalysts for the asymmetric Meerwein–Schmidt–Ponndorf–Verley–Oppenauer (MSPVO) reaction manifold

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Abstract—The development of aluminum-based catalysts for the asymmetric Meerwein–Schmidt–Ponndorf–Verley–Oppenauer (MSPVO) reduction/oxidation systems is reviewed with an emphasis on the mechanistic understanding of the origin for activity and selectivity in monometallic catalysts.

Contents

1. Introduction

The reduction of carbonyls to alcohols and the corresponding oxidation of alcohols to carbonyls constitute one of the most important classes of transformations in organic chemistry. With the demand for inexpensive, efficient, and clean synthetic strategies on the continuing increase, reduction and oxidation methodologies that address these needs are of utmost importance. In the mid-1920s Meerwein and Schmidt,[1] Ponndorf,[2] and Verley[3] independently discovered that ketones and aldehydes can be selectively reduced by 2-propanol to the corresponding alcohols in the presence of aluminum alkoxides [$Al(OR)_3$]. In 1937, Oppenauer[4] exploited the reversibility of the MSPV reaction to show that in the presence of aluminum *tert*-butoxide, acetone could act as a hydrogen acceptor in the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones. Together, the MSPV reduction and the Oppenauer oxidation constitute the modern Meerwein–Schmidt–Ponndorf–Verley–Oppenauer (MSPVO) reaction system (Scheme 1).

It is generally accepted that the classical MSPVO reaction proceeds through a hydride transfer pathway in

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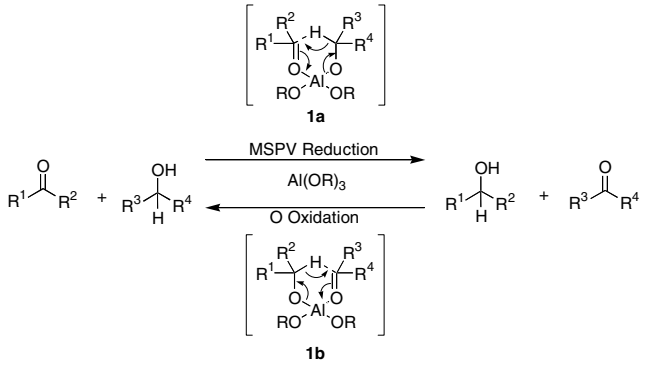
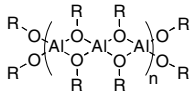


Scheme 1. The MSPVO reduction/oxidation system.

which the carbonyl substrate and secondary alcohol are both bound to the aluminum center in a *cis*-configuration.[5–8] The secondary alcohol serves as the hydride source and is coordinated as an alkoxide anion. The carbonyl group is believed to be activated upon its neutral, dative coordination to the Lewis acidic aluminum(III) metal center. Hydride transfer from the 2° carbon of the alcoholate to the carbonyl substrate via a six-membered, concerted transition state (Scheme 1, **1a** and **1b**) results in the reduction of the carbonyl and the simultaneous oxidation of the alcohol. The newly formed alkoxide ligand may leave the complex via an alcoholysis reaction in which a proton is abstracted from bulk alcohol in solution.[7]

Despite the initial success of the MSPVO reaction procedure in the manipulation of steroidal compounds, it did not find widespread utility in organic chemistry[8] after the 1950s outside of a few finely tuned and specific natural product syntheses.[9–14] This is partially due to the fact that under classical MSPVO reaction conditions, super-stoichiometric amounts (1–20 equiv relative to substrate) of the aluminum reagent are needed to obtain satisfactory yields in reasonable reaction times.[8] This sluggish activity was proposed to be a consequence of the highly aggregated state of the aluminum alkoxides, **2**.[15,16] It has been suggested that only the non-bridging terminal alkoxy groups in oligomeric Al-alkoxides are active in hydride transfer to carbonyl substrates.[15] As such, the low activity of these compounds can be attributed at least in part to the vast network of inactive bridging alkoxides[16–18] throughout these solids.[15]



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While several metal complexes, most notably those based on the lanthanides[19–21] and late transition metals,[22–29] have been shown to be active catalysts for the MSPVO reaction manifold, the classical aluminum-based MSPVO system is still extremely attractive as aluminum possesses many properties that make it an appealing metal in catalysis, including high abundance, low cost, a single stable oxidation state (III), and variable coordination number (3–6).[30] In recent years, catalytic variants of the aluminum-based MSPVO reduction/oxidation have emerged, deeming it once again an important methodology that is also environmentally friendly: it employs an inexpensive and innocuous metal catalyst, is highly chemoselective, and proceeds under relatively mild reaction conditions. Furthermore, as the common hydrogen source in the MSPV reduction is 2-propanol and the common hydrogen acceptor in the Oppenauer oxidation is acetone, the MSPVO reaction scheme utilizes easily separated, inexpensive, and readily available reductants and oxidants.

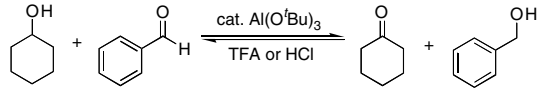
The stoichiometric MSPV reduction and Oppenauer oxidation have been reviewed by Wilds[31] and Djerassi,[32] respectively, covering this reaction manifold from its infancy to the early 1950s. Huskens et al. then summarized its progress up until the early 1990s,[8] followed in 2002 by Nishide and Node[33] who reviewed the asymmetric aspects of the MSPV reduction. Herein, we outline the development of MSPVO catalytic variants with emphasis toward those that are both catalytic and asymmetric. Relevant mechanistic details of the individual catalyst systems will be discussed when appropriate.

2. Aluminum-based MSPVO catalytic systems

Although the MSPVO reduction/oxidation reaction manifold was discovered over 70 years ago, it has not been until relatively recently that catalytic variants utilizing aluminum have been realized. These can be loosely divided into two classes: (1) protic acid-activated aluminum alkoxides and (2) 'well-defined' aluminum reagents in which the aluminum centers are complexed by multidentate ligands.

2.1. Protic acid-activated aluminum alkoxides as MSPVO catalysts

The initial discovery that protic acids can convert aluminum alkoxides into active MSPVO catalysts was reported by Rathke et al. in 1977.[15] They demonstrated that the addition of small amounts of trifluoroacetic acid (TFA) or hydrochloric acid (HCl) dramatically improves the activity of $Al(O^tBu)_3$ catalyst in the oxidation of cyclohexanol by benzaldehyde (Eq. 1).[15]



(1)

The equilibrium shown in Eq. 1 was established in one minute at 0 °C with 5 mol % $Al(O^tBu)_3$ in the presence of 2.5 mol % trifluoroacetic acid to give 88% yield of cyclohexanone. In contrast, when a stoichiometric amount of $Al(O^tBu)_3$ was used in the absence of acid, reaction 1 only reached equilibrium after 2–3 days at room temperature.[15]

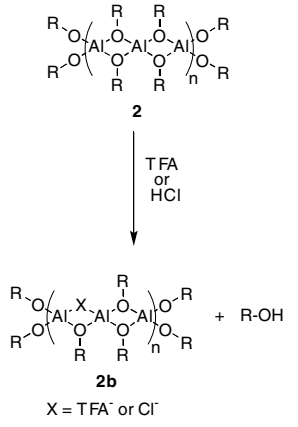
In the mid-1990s, Akamanchi and Noorani explored the acid-accelerated MSPV reaction using $Al(O^iPr)_3$ catalyst and either HCl or TFA as a co-catalyst.[34] The

Table 1. Catalytic MSPV reduction of carbonyls by ^{i}PrOH with TFA-activated Al($O^{i}Pr$)$_3$[34]

Entry	Carbonyl compound	Time (h)	Yield (%)
1	Benzaldehyde	0.75	93
2	3-Nitrobenzaldehyde	0.5	97
3	4-Methoxybenzaldehyde	4	61
4	3,4-Dimethoxybenzaldehyde	2	72
5	Acetophenone	22	44
6	Propiophenone	24	20
7	Cyclohexanone	6	80

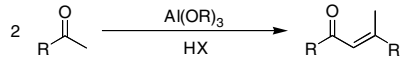
Al($O^{i}Pr$)$_3$/H^+ combination was found to be catalytically active for the reduction of a variety of aldehydes and ketones at room temperature (Table 1).[34]

As solid Al($O^{i}Pr$)$_3$ is known to be oligomeric in nature (vide supra) with bridging isopropoxy ligands,[16–18] Rathke proposed that the added protic acid replaces one or more of the bridging alkoxy ligands of **2** with a more electronegative anion to give **2b** (Eq. 2).[15] This makes the aluminum metal center more Lewis acidic[8,15] and enhances its coordination to the carbonyl substrate, thereby increasing the overall activity of the system.



(2)

While the Al(OR)$_3$/acid combination is the first example of a MSPVO catalyst based on aluminum, it has a large drawback for general use in organic synthesis. As an additive in the MSPVO reduction/oxidation manifold, strong acids, such as TFA or HCl, are not compatible with a variety of carbonyl substrates. Mixtures of aluminum alkoxides and protic acids are potent aldol condensation initiators and produce a significant amount of side products when enolizable substrates are employed (Eq. 3), thus decreasing the efficiency and chemoselectivity of the MSPVO reaction.[15]



(3)

2.2. 'Well-defined' aluminum complexes as MSPVO catalysts

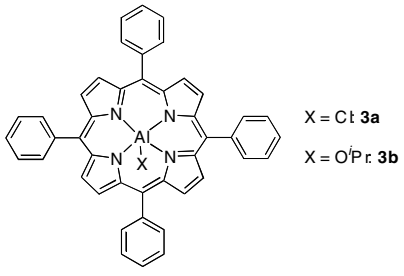
With the advent of environmentally friendly chemistry over the last two decades, there was a resurgence of interest in aluminum-based MSPVO chemistry, which resulted in the development of many new catalytic systems. Through appropriate choices of ligands, a variety of aluminum complexes have been prepared and their catalytic activities for the MSPVO reduction/oxidation screened.

Inoue et al. reported in 1988 that 5,10,15,20-tetraphenylporphyrin (TTP) aluminum(III) complexes **3a** and **3b** were active catalysts for the MSPV reduction of cyclohexanone and select aldehydes with 2-propanol (Table 2).[35] Interestingly, the MSPV reduction of 2-methylcyclohexanone catalyzed with 20 mol % **3a** resulted in a highly diastereotopic reduction with a *cis*/*trans* ratio of 93/7 (Table 2, entry 5). In comparison, the analogous reduction in the presence of a stoichiometric amount of Al($O^{i}Pr$)$_3$ yielded only 8% of the product in low diastereoselectivity (*cis*/*trans* = 46/54).[35]

The high *cis* selectivity of the 2-methylcyclohexanone reduction was attributed entirely to the steric environment of the TPP ligand. Although no evidence was provided for complete complexation of TTP to aluminum, it was postulated that a preferential coordination of the less hindered side of the ketone to **3a** led to predominately the formation of *cis*-2-methylcyclohexanol (Fig. 1).[35] The Inoue investigation was the first reported example of a catalytic, diastereoselective MSPV reduction initiated by a presumably discrete aluminum catalyst[36] and an achiral hydrogen source.

In the late 1990s, the Maruoka laboratory demonstrated that binuclear aluminum(III) complexes[37] **5a** and **5b** derived from bidentate phenoxide ligands could be used as catalysts for the MSPVO reaction.[38] Using 2-propanol as the hydrogen source, benzaldehyde was readily reduced to benzyl alcohol in the presence of a catalytic amount of **5a** (81% yield in 1 h, Table 3, entry 2). In stark contrast, when Al($O^{i}Pr$)$_3$ was used for the analogous reduction, the product was formed in a yield that at best was only commensurate to the amount of Al complex used (Table 3, entry 1).[38] This high catalytic activity of **5a** and **5b** toward the MPSV reduction was attributed to the bidentate nature of both complexes,

Table 2. Representative MSPV reductions of carbonyls with ^{i}PrOH using Al-complexes **3a** and **3b** at 30 °C[35]



Entry	Substrate	Catalyst	Time (h)	Conversion (%)
1	Cyclohexanone	**3a**	3	80
2	Hexanal	**3a**	3	84
3	Benzaldehyde	**3a**	3	40
4	Benzaldehyde	**3b**	3	6
5	2-Methylcyclohexanone	**3a**	3	93 (93/7 *cis*/*trans*)

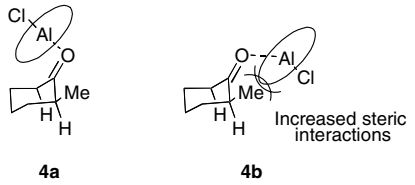
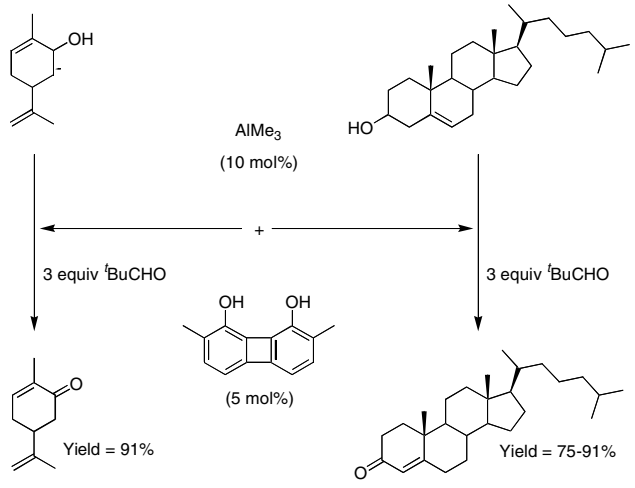


Figure 1. Schematic representation of the coordination of 2-methylcyclohexanone to the Al-porphyrin framework in the least sterically demanding arrangement **4a** and the more sterically demanding isomer **4b**. The oval representing the porphyrin ligand plane is not drawn to scale.

where double activation of the carbonyl group resulted in a highly active electrophilic species **6**.[38]

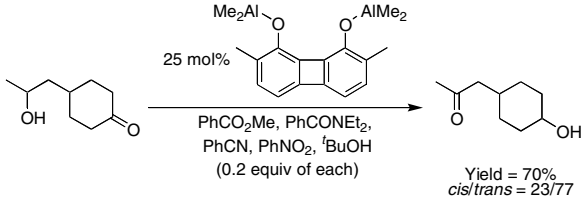
Maruoka et al. then demonstrated that in situ-generated bidentate aluminum complexes of type **5** could be used for the Oppenauer oxidation of a limited number of secondary alcohols. Using 5 mol % of dimeric aluminum complex, carveol was oxidized to carvone in 91% yield when 2,2-dimethylpropanal was used as the hydrogen acceptor. In addition, cholesterol could be oxidized with isomerization of the double bond to give the α,β-unsaturated product 4-cholesten-3-one in 75% yield under similar reaction conditions (Scheme 2).

Maruoka's bidentate aluminum catalysts similar to **5** could be applied to the simultaneous intramolecular MSPVO transformations of hydroxy carbonyl substrates. Thus, the aldehyde group in 4-(1-hydroxyethyl)-benzaldehyde, **A**, can serve as an active hydrogen acceptor for the oxidation of its benzyl alcohol moiety to give product **B** in 78% yield (Scheme 3).[39,40] Isolation of small amounts of the keto-aldehyde **C** and diol **D** suggests that an intermolecular hydride transfer pathway (Scheme 3, **8**) rather than an intramolecular route (Scheme 3, **7**) is operating.



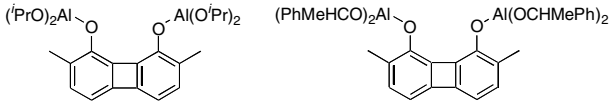
Scheme 2. The Oppenauer oxidation of carveol and cholesterol with 2,2-dimethylpropanal catalyzed by an in situ-generated bidentate Al-catalyst.

Inspired by these results, Maruoka et al. applied their bidentate catalyst system to the stereoselective intramolecular MSPVO conversion of 4-(2-hydroxypropyl) cyclohexanone to (4-hydroxycyclohexyl)methyl methyl ketone in 70% yield and a *cis*/*trans* ratio of 23/77 (Eq. 4). Reaction 4 was tolerant of various functional groups, including esters, amides, nitriles, nitro compounds, and tertiary alcohols.

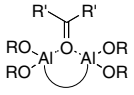


(4)

Table 3. MSPV reduction of carbonyl substrates with ^{i}PrOH catalyzed by bimolecular Al-complexes **5a** and **5b**[38]

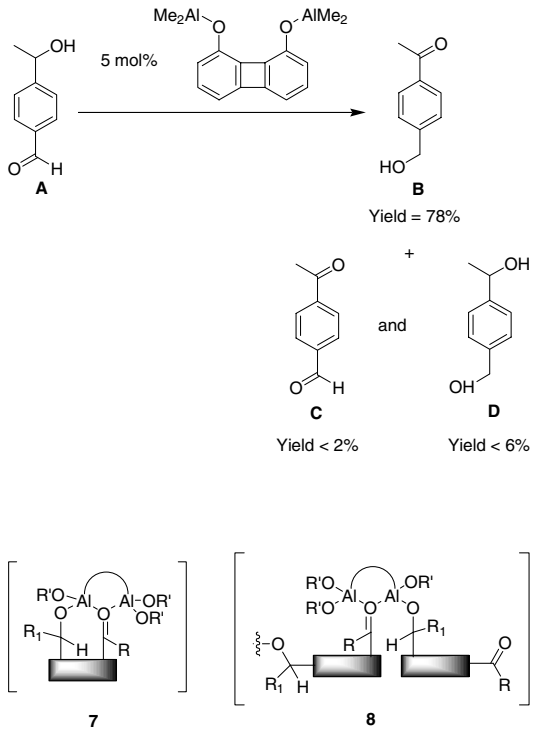


5a **5b**



6

Entry	Substrate	Al reagent (mol %)	Time (h)	Yield (%)
1	Benzaldehyde	$Al(O^{i}Pr)_3$ (10)	2	10
2	Benzaldehyde	**5a** (5)	1	81
3	α-Chloroacetophenone	$Al(O^{i}Pr)_3$ (100)	2	0
4	α-Chloroacetophenone	**5a** (5)	2	75
5	α-Chloroacetophenone	**5b** (5)	2	99
6	2-Undecanone	$Al(O^{i}Pr)_3$ (100)	5	0
7	2-Undecanone	**5a** (5)	5	50
8	2-Undecanone	**5b** (5)	5	73



Scheme 3. Simultaneous MSPVO transformations of hydroxy carbonyl substrates catalyzed by an in situ-generated Maruoka bidentate catalyst similar to **5**. Intermediates **7** and **8** depict the intra- and intermolecular hydride transfer pathways, respectively. The arc represents the diolate ligand framework and the shaded square is the aromatic portion of the substrate.

Recently, Lin et al. reported the development of novel dimeric aluminum alkoxide complexes **9a** and **9b**, which are active catalysts in the MSPV reduction of a variety of carbonyls by ^{i}PrOH (Table 4).[41,42] The sluggish activity of **9a** in the catalytic MSPV reduction of aldehydes could be attributed to over-coordination of the aluminum center in the transition state. Rather than undergoing an implied monomeric four-coordinate transition state as originally proposed[7] to be the optimal arrangement for the MSPV reduction, a less active, penta-coordinate species could be formed.[41] In support of this hypothesis, a dimeric complex of type **10** was obtained and crystallographically characterized when **9a** was reacted with excess 4-chlorobenzaldehyde (Fig. 2). Presumably, 2 equiv of the benzaldehyde were first reduced by the coordinated O^{i}Pr moieties of **9a**. An exchange of the as-generated acetones with two additional equivalents of 4-chlorobenzaldehyde resulted in **10**. As substitution of the *tert*-butyl groups of **9a** with the bulkier, more sterically demanding (CMe_2Ph) substituents resulted in a much more active MSPV pre-catalyst **9b** (Table 4), it is likely that this latter precursor does not favorably form penta-coordinate complexes of type **10** upon being exposed to organic carbonyls.[42]

2.3. Simple aluminum complexes as MSPVO catalysts

In 2001, we demonstrated a simple MSPV catalyst system based on low-aggregated[43] aluminum alkoxides that are generated in situ from reaction between simple organoaluminum complexes and ^{i}PrOH.[44] The low-aggregation state of the in situ-generated aluminum alkoxides was essential for catalytic activity. In all cases, the reduction of organic carbonyls to the respective alcohols proceeds in much shorter reaction times and in higher yields relative to those effected by Al(O^{i}Pr)$_3$

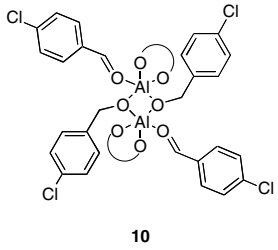
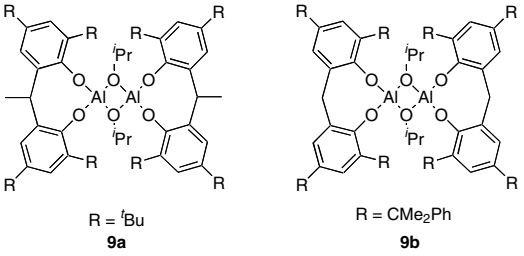


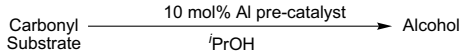
Figure 2. Schematic representation of **10** depicting alleged less-reactive penta-coordinate aluminum centers.

Table 4. The MSPV reduction of carbonyls with ^{i}PrOH catalyzed by Al-dimers **9a** and **9b**



Entry	Substrate	Al dimer	Time (h)	Conversion (%)
1	Benzaldehyde	**9a**[41]	24	93
2	Benzaldehyde	**9b**[42]	0.25	99
3	4-Methoxybenzaldehyde	**9a**[41]	24	60
4	4-Methoxybenzaldehyde	**9b**[42]	0.25	75
5	4-Nitrobenzaldehyde	**9a**[41]	0.50	99
6	4-Nitrobenzaldehyde	**9b**[42]	0.25	99
7	Acetophenone	**9b**[42]	0.25	86

Table 5. Catalytic MSPV reduction of carbonyls with ^{i}PrOH using simple alkylaluminum pre-catalysts at 10 mol % loading[44]

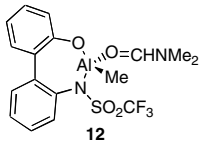


Entry	Substrate	Al pre-catalyst	Time (h)	Yield (%)
1	Cyclohexanone	a $AlMe_3$	3	82
		b $AlMe_2Cl$	2	96
		c $AlMeCl_2$	12	5
		d $Al(O^iPr)_3$	12	7
2	Benzaldehyde	a $AlMe_3$	2	91
		b $AlMe_2Cl$	1	60
		c $AlMeCl_2$	12	6
		d $Al(O^iPr)_3$	12	3
3	Acetophenone	a $AlMe_3$	12	51
		b $AlMe_2Cl$	12	55
		c $Al(O^iPr)_3$	12	0
4	α-Chloroacetophenone	a $AlMe_3$	12	99
		b $AlMe_2Cl$	12	65

itself (Table 5).[44] These results suggested that complex ligand frameworks are not absolutely necessary for the generation of an active aluminum-based MSPVO catalyst.

In addition to dimer **5**, Maruoka et al. have developed a new class of monomeric MSVPO catalysts based on the reactions between $AlMe_3$ and various acidic hydroxyl sulfonamides. While several ligand frameworks were screened, the optimal catalytic species incorporated 2-hydroxyl-2′-(perfluorooctanesulfonylamino)biphenyl as a bidentate ligand to form a seven-membered Al-containing metallocycle **11** as the catalytic precursor for the MSPV reduction of various ketones.[45] The **11**-catalyzed MSPV reduction of acetophenone to *sec*-phenethyl alcohol using ^{i}PrOH as the hydrogen source proceeded in good yield (76–85%) and short reaction time (5 h). Complex **11** was also an active catalyst for the MSPV reduction of various alkyl (Table 6, entries 1–3) and aromatic (Table 6, entries 4–6) ketone substrates to yield reduced product in good to excellent yields.

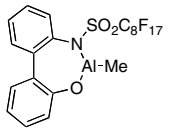
Maruoka et al. suggested a classical tetrahedral aluminum intermediate for the MSPV reductions of ketones catalyzed by **11** and its analogues.[45] To support this hypothesis, they prepared the tetrahedral amide-containing model complex **12** and characterized it thoroughly by X-ray diffraction.



12

Complex **11** can affect the catalytic Oppenauer oxidation of various alcohols using 2,2-dimethylpropanal as the hydrogen acceptor.[46] At low catalyst loadings of 1–3 mol % using 1.2–3 equiv of 2,2-dimethylpropanal, 2° aliphatic alcohols (Table 7, entries 4 and 5), 2° allylic alcohols (Table 7, entries 1, 2, and 6), and benzylic alcohols (Table 7, entries 3 and 7) were all readily oxidized to the corresponding carbonyls in short reaction times at ambient temperature. Primary alkyl alcohols (Table 7, entry 8) were not oxidized via this route.

Table 6. Catalytic MSPV reduction of ketone substrates with ^{i}PrOH catalyzed with 10 mol % of **11**[45]



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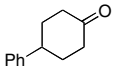
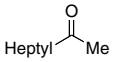
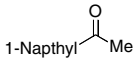
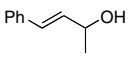
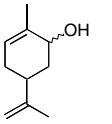
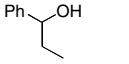
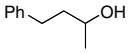
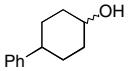
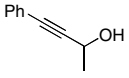
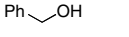
Entry	Substrate	Small-scale reaction		Scale-up (5-g) reaction	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1		0.5	99	2	99
2		5	97	5	94
3		5	92	5	91
4		3.5	85	5	82
5		5	99	5	98
6		5	97	9	95

As a control experiment, $AlMe_3$ was used as the catalyst at 10 mol % loading in the Oppenauer oxidation of *trans*-4-phenyl-3-buten-2-o1 to the corresponding *trans*-4-phenyl-3-buten-2-one. Even after 18 h under similar conditions, this oxidation proceeded in only 27% yield. The authors attributed the drastic difference in reactivity between $AlMe_3$ and **11** to the electron-withdrawing nature of the ligand in the latter complex, suggesting that a highly Lewis-acidic aluminum species is needed for the generation of an active MSPVO catalyst.[46]

In addition to 2,2-dimethylpropanal, acetone could be used as an effective hydrogen acceptor in the **11**-catalyzed Oppenauer oxidation of terpenoids and steroids without generating aldol byproducts.[46] At low catalyst loading (5 mol %) and using only 1.2 equiv of acetone, carveol was oxidized to 2-carvone in 83% yield in only 2 h at ambient temperature. The oxidation of α-jonol to α-ionone proceeded readily under analogous reaction conditions; and 4-cholesten-3-one was readily available from the Oppenauer oxidation of corresponding alcohol (cholest-4-en-3β-ol) when 3 equiv of acetone was used.[46] In contrast, under classical MSPVO conditions, where solid aluminum alkoxides were used in excess, the oxidation of carveol to 2-carvone was only accomplished under a large excess of acetone (50–200 fold) at refluxing temperatures.[32]

Table 7. Catalytic Oppenauer oxidation of various alcohols with **11**[46]

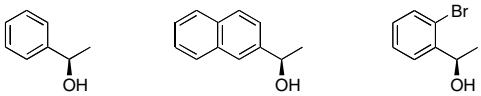
Entry	Alcohol	Equiv of ^{t}BuCHO	Time (h)	Yield (%)
1		1.2	1	94
2		1.2	1	94
3		1.2	1	87
4		1.2	5	93
5		1.2	3	84
		3	1	90
6		1.2	3	80
7		3	1	82
8		1.2	3	0

3. Aluminum-based catalytic asymmetric MSPVO reactions

As mentioned above, the asymmetric MSPVO reactions utilizing stoichiometric amounts of aluminum reagents were reviewed extensively by Nishide and Node[33] and will not be revisited here. In this section, we will discuss recent progress in the catalytic asymmetric MSPVO reaction, starting with catalysts that use stoichiometric chiral alcohols as the hydrogen transfer agent to the development of systems incorporating chiral ligands and achiral hydrogen sources/oxidants.

3.1. Catalytic asymmetric MSPVO reactions utilizing chiral hydrogen sources

Using complex **5b** (5 mol %) as catalyst and enantiopure *sec*-phenethyl alcohol (*R*)-**E** as the hydrogen source, Maruoka et al. were able to reduce α-chloroacetophenone with good yield (82%) and moderate enantiomeric excess (ee) (54%).[38] When the steric bulk of the hydrogen source was increased, by using (*R*)-(+)-α-methyl-2-naphthylmethanol (*R*)-**F** as the chiral hydrogen source, the ee of the reduced product increased to 70%, albeit at the expense of yield (58%). The use of enantiopure *ortho*-brominated *sec*-phenethyl alcohol (*R*)-**G** further increased the enantioselectivity to 82%, although the yield was still moderate (51%). The selectivity of the reaction was attributed to the dimeric nature of the aluminum complex.



(*R*)-**E** (*R*)-**F** (*R*)-**G**

We reported in 2001 that the use of $AlMe_3$ as the catalytic precursor (10 mol %) can affect the enantioselective reduction of α-chloroacetophenone by either (*R*)-**F** or (*R*)-**G,** giving chiral products with ees of 68% and 81–86%, respectively (Table 8, entries 4 and 6, respectively).[44] Furthermore, the $AlMe_2Cl$-catalyzed MSPV reduction of 2-methylcyclohexanone using ^{i}PrOH as the hydrogen source yielded 2-methylcyclohexanol with a *cis*/*trans* ratio of 80/20 both with and without TTP as a ligand additive (Table 8, entries 1 and 2, respectively). This set of experiments demonstrated that complex ligand frameworks were not absolutely needed for stereoselective aluminum-based MSPV reductions.

3.2. Catalytic asymmetric MSPVO reactions utilizing achiral hydrogen sources

In 2002, we reported the first Al-catalyzed asymmetric MSPV reduction that utilized an achiral hydrogen source. The use of enantiopure 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) as a 1:1 chiral additive to $AlMe_3$ pre-catalyst allowed for the convenient ligand-accelerated[47] reduction of a variety of aromatic ketones by ^{i}PrOH, affording moderate to high yields (32–99%) and moderate to good enantioselectivities (32–83%) (Table 9).[48]

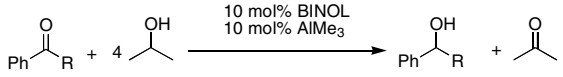
Although increasing the sterics of the carbonyl group led to an increased ee, it did so at the expense of yield (Table 9, entries 1–4). Highest yield and selectivity were observed for carbonyl substrates which contain an α-halogen (Table 9, entries 5 and 6). While coordinating groups such as α-methoxy led to high yield of reduction, the selectivity was much lower than those obtained for substrates containing α-halogen substituents.[48]

We recently applied the (BINOL)Al catalyst to the kinetic resolution of various 2° alcohol racemates utilizing cyclohexanone as the Oppenauer oxidant.[49] As with the corresponding MSPV reduction, the kinetic resolution of the benzyl alcohol racemates gave the highest selectivity factor (*s*) when an α-halogen was incorporated in the alkyl group of the substrate (Table 10, entry 2).

Table 8. Comparison of stereoselective MSPV reductions using simple organoaluminum catalysts and complexed aluminum[44]

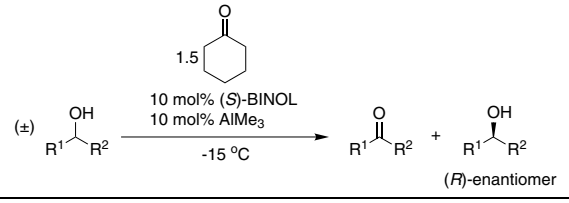
Entry	Substrate	Al reagent	Ligand	Hydride source	Product selectivity	
					cis/*trans*	ee (%)
1	2-Methylcyclohexanone	$AlMe_2Cl$	5,10,15,20-Tetraphenylporphyrin	^{i}PrOH	20/80	—
2	2-Methylcyclohexanone	$AlMe_2Cl$	None	^{i}PrOH	20/80	—
3	α-Chloroacetophenone	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol	(*R*)-**F**	—	70
4	α-Chloroacetophenone	$AlMe_3$	None	(*R*)-**F**	—	68
5	α-Chloroacetophenone	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol	(*R*)-**G**	—	82
6	α-Chloroacetophenone	$AlMe_3$	None	(*R*)-**G**	—	81–86

Table 9. The asymmetric MSPV reduction with ^{i}PrOH catalyzed by the in situ-generated complex between (*R*)-BINOL and $AlMe_3$[48]



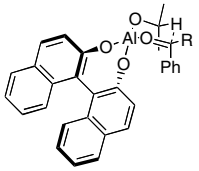
Entry	R	Yield (%)	ee (%)
1	CH_3	54	32
2	CH_2CH_3	30	50
3	$CH(CH_3)_2$	20	61
4	$CH_2CH(CH_3)_2$	32	53
5	CH_2Cl	99	80
6	CH_2Br	99	83
7	CH_2OCH_3	95	43

Table 10. The kinetic resolution of alcohol racemates using cyclohexanone as the Oppenauer oxidant and (*S*)-BINOL/$AlMe_3$ catalyst system[49]

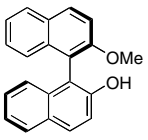


Entry	R^1	R^2	*s* factor
1	Ph	Et	6.5
2	Ph	CH_2Br	21.1
3	1-Naphthyl	Me	2.6
4	2-Naphthyl	Me	2.4
5	1-Indanol		1.8
6	α-Tetralol		1.2
7	Ph_2CH	Me	4.8
8	Cy	Me	1.4

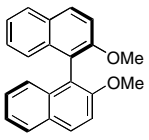
Since a 1:1 ratio of BINOL and $AlMe_3$ was optimal for the MSPV reduction, we proposed the monomeric tetracoordinate (BINOL)Al complex, **13**, as the active catalytic species for this reaction, which operates through a concerted hydride transfer pathway. Further support of this optimal transition state was gained through comparative studies with ligands (*R*)-**I**, (*R*)-**II**, and (*R*)-**III**, all of which do not allow for a tetrahedral aluminum geometry. In all cases, a dramatic reduction in the ee of product was noted.[48]



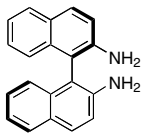
13



(*R*)-**I**

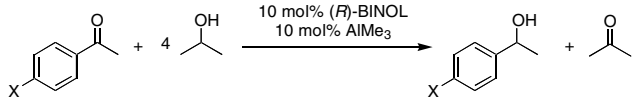


(*R*)-**II**



(*R*)-**III**

Table 11. Electronic effect on the asymmetric MSPV reduction with ^{i}PrOH catalyzed by the in situ-generated complex between (*R*)-BINOL and $AlMe_3$[48]



Entry	X	Product	
		Yield (%)	ee (%)
1	CH_3	44	30
2	H	54	32
3	F	55	30
4	Cl	70	30
5	Br	70	30

Consistent with the hypothesis that the Lewis-acidic aluminum center serves to activate the ketone substrate, decreasing the electron density on the aromatic ring of a series of *para*-substituted aromatic ketones increased the yield of the corresponding alcohol, although no significant change in product ee was observed (Table 11).[48]

To verify the aforementioned concerted hydride transfer proposal, we carried out a detailed mechanistic study of the tetrahedrally constrained (BINOL)Al-catalyzed MSPV reduction using both experiments and density functional theory.[50] While both hydridic and radical pathways were also considered, the theoretically and experimentally determined values for the deuterium isotope effect, energetic parameters, and enantioselectivities strongly correlated to a mechanism involving a direct and concerted hydride transfer.[50]

4. Conclusions

Several catalytic variants of the Meerwein–Schmidt–Ponndorf–Verley–Oppenauer reduction/oxidation manifold have emerged over the last decade, making this reaction system a very attractive option in the arena of environmentally friendly synthetic methodologies. The development and application of new ligands for the MSPVO chemistry, coupled with a detailed understanding of mechanistic issues, will significantly advance it into a practical and highly selective tool in synthetic chemistry.

Acknowledgments

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References

1. Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem* **1925**, *444*, 221–238.

2. Ponndorf, W. *Z. Angew. Chem.* **1926**, *39*, 138–143.
3. Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871–874.
4. Oppenauer, R. V. *Rec. Trav. Chim.* **1937**, *56*, 137–144.
5. Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414–421.
6. Moulton, W. N.; Atta, R. E. V.; Ruch, R. R. *J. Org. Chem.* **1961**, *26*, 290–292.
7. Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425–1429.
8. de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017.
9. Ramig, K.; Kuzemko, M. A.; Parrish, D.; Carpenter, B. K. *Tetrahedron Lett.* **1992**, *33*, 6279–6282.
10. Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Heterocycles* **1981**, *15*, 377–379.
11. Bevinakatti, H. S.; Badiger, V. V. *J. Heterocycl. Chem.* **1980**, *17*, 1701–1703.
12. Chinn, L. J.; Salamon, K. W. *J. Org. Chem.* **1979**, *44*, 168–172.
13. Jones, R. A.; Webb, T. C. *Tetrahedron* **1972**, *28*, 2877–2879.
14. Rice, K. C.; Wilson, R. S. *J. Med. Chem.* **1976**, *19*, 1054–1057.
15. Kow, R.; Nygren, R.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 826–827.
16. Fieggen, W.; Gerding, H. *Recl. Trav. Chim. Pays-Bas.* **1970**, *89*, 175–185.
17. Sauls, F. C.; Interrante, L. V.; Jiang, Z. *Inorg. Chem.* **1990**, *29*, 2989–2996.
18. Rogers, J. H.; Apblett, A. W.; Cleaver, W. M.; Tyler, A. N.; Barron, A. R. *J. Chem. Soc., Dalton Trans.* **1992**, 3179–3187.
19. Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045–2049.
20. Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801.
21. Molander, G. A.; McKie, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 5821–5822.
22. Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490–1492.
23. Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2005**, *24*, 3422–3433.
24. Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.
25. Inoue, S.; Nomura, K.; Hashiguchi, S.; Noyori, R.; Izawa, Y. *Chem. Lett.* **1997**, 957–958.
26. Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, *68*, 1601–1602.
27. Chowdhury, R. L.; Baeckvall, J. E. *J. Chem. Soc., Chem. Comm.* **1991**, 1063–1064.
28. Krasik, P.; Alper, H. *Tetrahedron* **1994**, *50*, 4347–4354.
29. Vinzi, F.; Zassinovich, G.; Mestroni, G. *J. Mol. Catal.* **1983**, *18*, 359–366.
30. Banister, A. J.; Wade, K. *The Chemistry of Aluminum, Gallium, Indium, and Thallium*; Pergamon: Elmsford NY, 1975, pp 180.
31. Wilds, A. L. *Org. React.* **1944**, *2*, 178–223.
32. Djerassi, C. *Org. React.* **1951**, *6*, 207–272.
33. Nishide, K.; Node, M. *Chirality* **2002**, *14*, 759–767.
34. Akamanchi, K. G.; Noorani, V. R. *Tetrahedron Lett.* **1995**, *36*, 5085–5088.
35. Konishi, K.; Kazuyuki, M.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1988**, 643–645.
36. The Al(TPP) complex was generated in situ by adding $AlMe_2Cl$ to the free-base TPP ligand. Characterization data were not provided.
37. Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307–11308.
38. Ooi, T.; Miura, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2347–2349.
39. Ooi, T.; Itagaki, Y.; Miura, T.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2137–2138.
40. Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* **2002**, 279–291.
41. Ko, B.; Wu, C.; Lin, C. *Organometallics* **2000**, *19*, 1864–1869.
42. Liu, Y.-C.; Ko, B.-T.; Huang, B.-H.; Lin, C.-C. *Organometallics* **2002**, *21*, 2066–2069.
43. Graves, C. R.; Nguyen, S. T., unpublished results.
44. Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391–2393.
45. Ooi, T.; Ichikawa, H.; Maruoka, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3610–3612.
46. Ooi, T.; Otsuka, H.; Miura, T.; Ichikawa, H.; Maruoka, K. *Org. Lett.* **2002**, *4*, 2669–2672.
47. Graves, C. R.; Nguyen, S. T. *Abstracts of Papers*, 228th ACS National Meeting, Philadelphia, PA, United States, August 22–26, 2004.
48. Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1020–1022.
49. Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *Abstracts of Papers*, 39th NOS National Meeting, Salt Lake City, UT, United States, June 12–16, 2005.
50. Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796–14803.