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[9] Fluorescence quenching (supramolecular array/porphyrin mixture at the same optical density): **5a** (ca. 87 % in toluene, ca. 93 % in CCl_4), **5b** (> 90 % in $CHCl_3$ or mineral oil), **9a** (14 % in toluene), **10a** (18 % in toluene). The complete photophysical characterization of these systems will be reported elsewhere.

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Highly Efficient, Catalytic Meerwein – Ponndorf – Verley Reduction with a Novel Bidentate Aluminum Catalyst**

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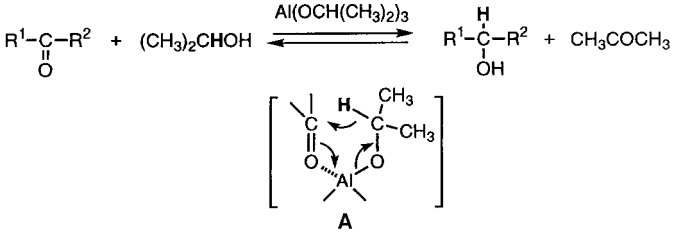
The Meerwein – Ponndorf – Verley (MPV) reaction, named after the independent originators, involves the chemoselective reduction of carbonyl substrates with aluminum alkoxides, generally $Al(OiPr)_3$, as catalyst and *i*PrOH as hydride source.[1–3] In the MPV reduction, a reversible hydride transfer from the alcoholate to a carbonyl acceptor via a six-membered transition state [**A**] is initiated by the activation of the carbonyl group by coordination to the Lewis acidic aluminum center (Scheme 1).[4] Acetone is formed as a volatile side product, which is easily removed during the reaction. Advantages of the MPV reduction include chemoselectivity, mild reaction conditions, operational simplicity, safe handling, and ready adaptation both in the laboratory and on a large scale.[5]



Scheme 1. MPV reduction of carbonyl compounds with $Al(OiPr)_3$ in *i*PrOH, which proceeds via transition state **A**.

Nonetheless, there are several practical problems with the MPV reduction such as the need for an excess of alcohol as hydride source, low reaction rate, formation of condensation products, and need for higher reaction temperatures so that the concurrent removal of acetone shifts the equilibrium towards the formation of alcohol. The most important side reactions are the aldol condensation and the Tishchenko reaction; the latter leads to the formation of carboxylic esters, especially in the case of the more reactive aldehydes.[6] Accordingly, various modifications of the MPV reduction have been developed in order to overcome these disadvantages. The more recent improvements are the use of catalytically active lanthanide alkoxides,[7] microwave irradiation,[8] and the addition of CF_3CO_2H to $Al(OiPr)_3$ to accelerate the reduction.[9] Herein we report the highly accelerated MPV reduction of carbonyl substrates with a bidentate aluminum catalyst. The realization of this modern MPV reduction is crucially dependent on the effective use of our recently developed bidentate Lewis acid chemistry.[10]

The typical MPV reduction of carbonyl substrates proceeds quite reluctantly. For example, reduction of benzaldehyde in CH_2Cl_2 with $Al(OiPr)_3$ (1 equiv) at room temperature for 1 h gave rise to benzyl alcohol in 34 % yield.[11] When the reaction was carried out in CH_2Cl_2 with *i*PrOH (1 equiv) and a catalytic amount of $Al(OiPr)_3$ (10 mol %) at room temperature for 2 h, benzyl alcohol was obtained in only 10 % yield (Table 1). Under similar reduction conditions, ketone substrates (e.g., 4-phenylcyclohexanone and 2-undecanone) were totally unreactive, and most of the starting material was recovered. In marked contrast, however, use of the bidentate aluminum catalyst **1** in the reduction of benzaldehyde produced the benzyl alcohol at room temperature instantaneously and almost quantitatively (Scheme 2). Catalyst **1** is generated in situ from 2,7-dimethyl-1,8-biphenylenediol, Me_3Al (2 equiv), and *i*PrOH (4 equiv). Moreover, even with 5 mol % of **1** the reduction proceeds quite smoothly at room temperature to furnish benzyl alcohol in 81 % yield after 1 h. This remarkable efficiency can be ascribed to the double

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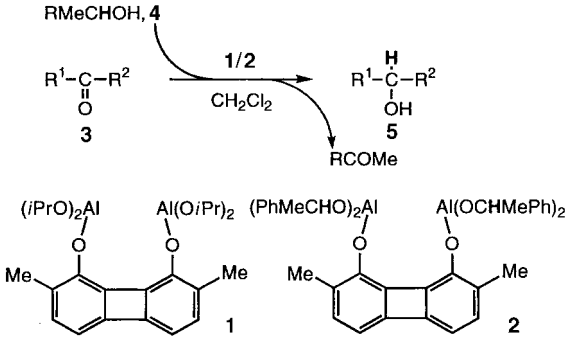
Table 1. Catalytic MPV reduction of carbonyl substrates with **1** or **2**.

Substrate	Al reagent (mol %)	Hydride source (equiv)	*t* [h]	Yield [%][a]
PhCHO	$Al(OiPr)_3$ (100)	–	1	34
PhCHO	$Al(OiPr)_3$ (10)	*i*PrOH (1)	2	10
PhCHO	**1** (100)	–	(5 min)	99
PhCHO	**1** (5)	*i*PrOH (1)	1	81
PhCHO	**1** (5)	*i*PrOH (3)	1	96
$PhCH(CH_2)_4C{=}O$	$Al(OiPr)_3$ (100)	–	1	(trace)
$PhCH(CH_2)_4C{=}O$	**1** (5)	*i*PrOH (1)	1	91
$PhCH(CH_2)_4C{=}O$	**1** (5)	*i*PrOH (1)	2	99
$PhC(O)CH_2Cl$	$Al(OiPr)_3$ (100)	–	2	–[b]
$PhC(O)CH_2Cl$	**1** (5)	*i*PrOH (1)	2	75
$PhC(O)CH_2Cl$	**1** (5)	*i*PrOH (1)	10	89
$PhC(O)CH_2Cl$	**2** (5)	PhMeCHOH (1)	2	99
$CH_3(CH_2)_8COCH_3$	$Al(OiPr)_3$ (100)	–	5	–[b]
$CH_3(CH_2)_8COCH_3$	**1** (5)	*i*PrOH (3)	5	50
$CH_3(CH_2)_8COCH_3$	**2** (5)	PhMeCHOH (1)	5	73
$CH_3(CH_2)_8COCH_3$	**2** (5)	PhMeCHOH (3)	5	89
$CH_3(CH_2)_8COCH_3$	**2** (5)	PhMeCHOH (6)	5	99
$PhCH{=}CHCOCH_3$	**1** (5)	*i*PrOH (1)	5	31[c]
$PhCH{=}CHCOCH_3$	**2** (5)	PhMeCHOH (6)	5	70[c]

[a] Yield of isolated product. [b] No reaction. [c] Yield of 1,2-reduction product.

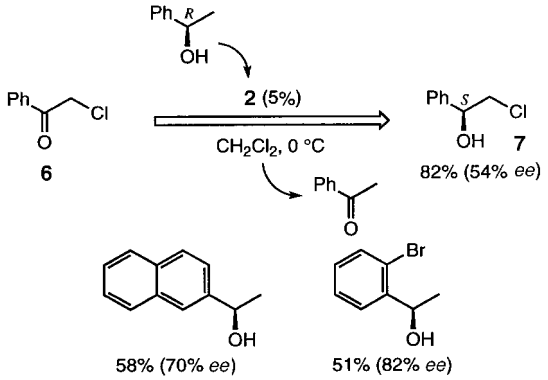


Scheme 2. Catalytic MPV reduction of aldehydes and ketones with **1** or **2**.

electrophilic activation of carbonyl groups by the bidentate aluminum catalyst.[12]

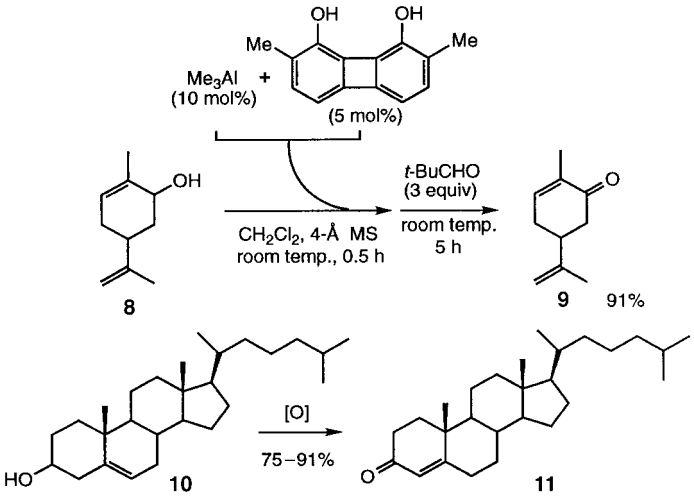
Other selected examples are listed in Table 1. In addition to aldehydes, both cyclic and acyclic ketones can be reduced equally well. *sec*-Phenethyl alcohol (**4**, R = Ph) is a more effective hydride source than *i*PrOH. This finding prompted us to examine the enantioselective MPV reduction of unsymmetrical ketones with chiral alcohols in the presence of catalyst **2** (Scheme 3).[13] Indeed, treatment of 2-chloroacetophenone (**6**) with optically pure (*R*)-(+)-*sec*-phenethyl alcohol (1 equiv) under the influence of **2** at 0 °C for 10 h afforded (*S*)-(+)-2-chloro-1-phenylethanol (**7**) with moderate asymmetric induction (82% yield, 54% *ee*).[14] Switching chiral alcohols from (*R*)-(+)-*sec*-phenethyl alcohol to (*R*)-(+)-*α*-methyl-2-naphthylmethanol and (*R*)-(+)-*sec*-*o*-bromophenethyl alcohol further enhanced the optical yields of **7** to 70 and 82% *ee*, respectively.[14, 15]

The present approach is applicable to the reverse reaction of the MPV reduction, that is, the Oppenauer oxidation.[16, 17] We have successfully developed a highly accelerated Oppenauer oxidation system using a bidentate aluminum catalyst of type **1** and **2**. This modified, catalytic system effectively oxidizes a variety of secondary alcohols to the corresponding



Scheme 3. Enantioselective MPV reduction with chiral secondary alcohols as hydride source.

ketones. For example, sequential addition of a 1M solution in hexane of Me_3Al (10 mol %) and carveol (**8**) to 2,7-dimethyl-1,8-biphenylenediol (5 mol %) in CH_2Cl_2 at room temperature in the presence of 4-Å molecular sieves and subsequent treatment with pivalaldehyde (3 equiv) at room temperature for 5 h provided carvone (**9**) in 91% yield. Under similar oxidation conditions, cholesterol (**10**)[18] was converted into 4-cholesten-3-one (**11**) in 75% yield (91% yield with 5 equiv of *t*BuCHO, Scheme 4).



Scheme 4. Catalytic Oppenauer oxidation of secondary alcohols with bidentate aluminum catalyst/pivalaldehyde system.

Experimental Section

MPV reduction of 4-phenylcyclohexanone: 2,7-Dimethyl-1,8-biphenylenediol (10.7 mg, 0.05 mmol) and predried, powderized 4-Å molecular sieves (ca. 60–70 mg) were placed in a dry two-neck flask with a stirring bar under argon, and freshly distilled CH_2Cl_2 (5 mL) was introduced. The suspension was carefully degassed and a 1M solution of Me_3Al (100 μL, 0.1 mmol) in hexane was added dropwise at room temperature. After the reaction mixture was stirred for 30 min, *i*PrOH (92 μL, 1.2 mmol) was added, and the stirring was continued for an additional 30 min. The resulting mixture was then treated with a solution of 4-phenylcyclohexanone (174 mg, 1.0 mmol) in CH_2Cl_2 and stirred at room temperature for 1 h. The reaction was quenched with 1N HCl, and the mixture was extracted with diethyl ether. The combined organic extracts were then dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column

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chromatography on silica gel (CH_2Cl_2 as eluant) gave a *cis*/*trans* mixture of 4-phenyl-1-cyclohexanol (159 mg, 0.91 mmol, 91 % yield; *cis*:*trans* = 23:77).

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The Family Approach to the Resolution of Racemates **

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A cornerstone of stereochemistry is the resolution of tartaric acid by Louis Pasteur.[1, 2] This conversion of a racemate with a chiral resolving agent and subsequent separation of the mixture of diastereomers formed is known as the "classical method of resolution",[3] and remains, 150 years after Pasteur, a paradigm of trial and error.[4] Despite many attempts,[3] neither computer-assisted modeling,[5] detailed examination of the crystal structure data of diastereomeric salts,[6] study of the energy differences of diastereomeric salts,[7] nor empirical correlations[8] have led to a hypothesis, let alone a theory, on which to base a predictable resolution technique.

All too aware of these problems on the basis of long experience and motivated by a need to develop fast and reliable protocols, we considered the combinatorial approach, a recent technique that has shown promise in the search for lead compounds in drug design.[9] A rudimentary application of such methodology led to the remarkable results reported here.

The standard technique for the resolution of a racemate entails the addition of one chiral resolving agent to a racemate followed by a suitable waiting period in order to observe crystallization of one diastereomeric salt. We hoped that the simultaneous addition of several resolving agents might shorten the time required for the hit-and-miss method of finding a resolving agent. The addition of more than one resolving agent could result in the precipitation of the least soluble diastereomeric salt, thus obviating the need for repetition of the process of resolution with one resolving agent at a time. To our great surprise, the simultaneous addition of more than one member of a "family" of resolving agents (for a definition, see below) to a solution of a racemate usually causes very rapid precipitation of a crystalline diastereomeric salt in good to high enantiomeric purity and yield. The results from some of the more than two hundred successful experiments carried out during the past year[10] are listed in Tables 1 and 2. In virtually all cases examined both the yields and enantiomeric excesses (*ee*) were superior to those obtained by the classical approach (compare entry 55 with entry 53).

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