Practical Approach to the Meerwein–Ponndorf–Verley Reduction of Carbonyl Substrates with New Aluminum Catalysts[**]

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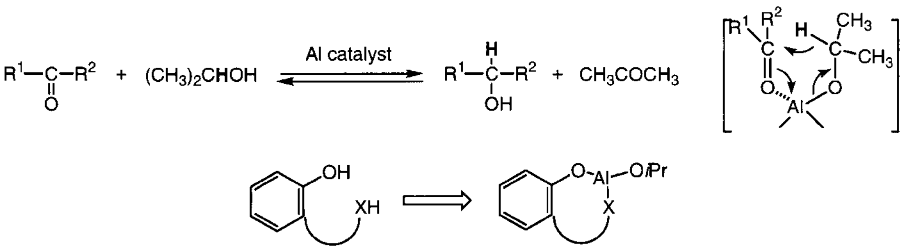


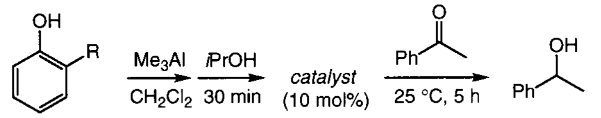
Scheme 1. General schemes for Meerwein–Ponndorf–Verley reduction of carbonyl compounds and the development of new aluminum catalysts.

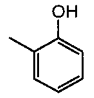
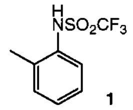
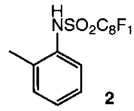
The Meerwein–Ponndorf–Verley (MPV) reaction, which involves a reversible hydride transfer via a six-membered transition state, has long-been recognized as a particularly mild reduction method that has several attractive features.[1–3] The reaction is operationally very simple, uses inexpensive, nontoxic, and nonhazardous reagents such as $Al(O\mathit{i}Pr)_3$ and *i*PrOH, and is compatible with a broad range of functional groups present in the substrate.

However, these advantages seem to be canceled out by the usual need for relatively drastic reaction conditions because of the poor reactivity of the traditional $Al(O\mathit{i}Pr)_3$/*i*PrOH catalyst system, for which continuous removal of acetone is necessary to shift the equilibrium and hence undesirable side reactions seem inevitable. Accordingly, a number of modern variants of metal alkoxide/hydride source combinations have been elaborated to allow the classical methodology to regain an appropriate place in organic synthesis.[4–7] Although our recently introduced catalytic procedure with bidentate aluminum alkoxides certainly contributed to such an endeavor, it unfortunately requires *sec*-phenethyl alcohol as a hydride donor for smooth reduction of simple acyclic aliphatic ketones.[8] This constitutes a major difficulty (especially in the reduction of aromatic ketones), and prompted us to make further effort to bring out the inherent potential in the MPV reduction for practical use. Herein we report our preliminary results on the development of new aluminum alkoxides that can be employed for the efficient catalytic MPV reduction of various ketone substrates (including aromatic ketones). These reactions, which proceed under mild reaction conditions and in which *i*PrOH functions as a convenient hydride source, provide a simple yet practical method for carbonyl reduction.

Our strategy for the development of a readily accessible, highly active aluminum catalyst was based on the modification of simple aluminum phenoxide through introduction of an additional heteroatom-containing functionality on the *ortho* position of the parent phenol aromatic ring as schematically illustrated in Scheme 1. Attempted reduction of acetophenone as a representative substrate in the presence of diisopropoxyaluminum phenoxide (10 mol%) (prepared in situ from phenol, Me_3Al, and *i*PrOH) and *i*PrOH as a hydride source (5 equiv) in CH_2Cl_2 at 25 °C for 5 h resulted in total recovery of the starting ketone (Table 1, entry 1), and use of salicylic acid as an aluminum ligand gave none of the desired *sec*-phenethyl alcohol (Table 1, entry 2). Although the reactivity was slightly enhanced by aluminum isopropoxides derived from catechol and *o*-(methanesulfonylamino)phenol, it was far from a synthetically satisfactory level (Table 1, entries 3 and 4). However, use of the phenol possessing a trifluoromethanesulfonamide functionality improved the yield of *sec*-phenethyl alcohol (30%) and a similar result was obtained with the 2,2′-biphenol-based catalyst (46%) (Table 1, entries 5 and 6),[9] which led us to consider the possibility of combining the two structural characteristics. The synthesis of 2-hydroxy-2′-(trifluoromethanesulfonylamino)biphenyl (**1**) was thus pursued starting from phenol. Interestingly, treatment of acetophenone with 10 mol% of catalyst, prepared from **1**, Me_3Al, and *i*PrOH, in CH_2Cl_2 at 25 °C for 5 h produced the corresponding secondary alcohol in 65% yield (Table 1, entry 7). Here, tuning of the perfluoroalkyl group of the sulfonamide moiety afforded a beneficial effect on the catalyst activity. Thus, the reaction under the influence of the

Table 1. Catalytic MPV reduction of acetophenone with various aluminum catalysts.[a]



Entry	R	*i*PrOH [equiv]	Yield [%][b]
1	H	5	n.r.[c]
2	COOH	5	n.r.[c]
3	OH	5	8
4	$NHSO_2CH_3$	5	9
5	$NHSO_2CF_3$	5	30
6		5	46
7	 **1**	5	65
8	 **2**	5	76
9	**2**	10	85

[a] The MPV reduction of acetophenone was conducted with several aluminum catalysts (10 mol%) and *i*PrOH (distilled from CaH_2) in freshly distilled CH_2Cl_2 at 25 °C for 5 h. [b] Yield of isolated product. [c] n.r. = no reaction.

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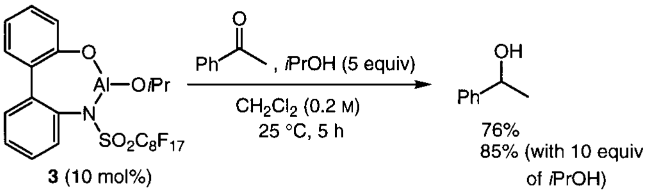
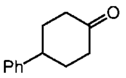
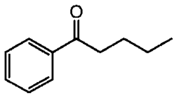
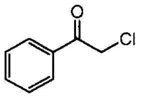
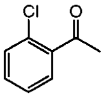
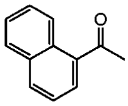
aluminum isopropoxide **3** (Scheme 2), which was derived from 2-hydroxy-2′-(perfluorooctanesulfonylamino)biphenyl (**2**), gave rise to *sec*-phenethyl alcohol in 76% yield and, eventually, the yield of the alcohol was improved to 85% by using 10 equivalents of *i*PrOH (Table 1, entries 8 and 9, respectively).[10]



Scheme 2. Efficient catalytic MPV reduction of acetophenone in the presence of the new aluminum alkoxide **3**.

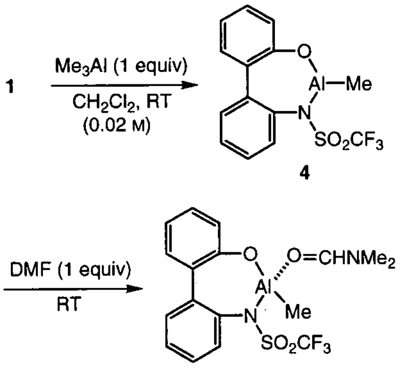
A variety of ketone substrates were examined for this optimized catalytic MPV reduction with **3** and the results are summarized in Table 2. As expected, cyclic ketones such as 4-phenylcyclohexanone can be reduced instantaneously to 4-phenylcyclohexanol quantitatively (*cis*/*trans* = 17:83) (Table 2, entry 1). Simple aliphatic ketones were also found to be efficiently converted to the corresponding secondary alcohols in excellent yields (Table 2, entries 2 and 3). Moreover, the present catalytic system based on the newly developed aluminum catalyst allows smooth hydride transfer from *i*PrOH to various aromatic ketones (Table 2, entries 4–7).

Table 2. Catalytic MPV reduction of ketone substrates with new aluminum catalyst **3**[a] and scale-up experiments with 5 g of starting ketones.[b]

Entry	Substrate	Conditions [°C]	Conditions [h]	Yield[c] [%]	Scale-up reaction conditions [°C]	Scale-up reaction conditions [h]	Scale-up reaction yield [%][c]
1		25	0.5	99[d]	25	2	99[d]
2	$CH_3(CH_2)_6COCH_3$	25	5	97	25	5	94
3	$(CH_3(CH_2)_3)_2C{=}O$	25	5	92	25	5	91
4		25	3.5	85	25	5	82
5		25	5	99	25	5	98
6		25	1	99	25	3.5	99
7		25	5	97	25	9	95

[a] The MPV reduction of various ketone substrates was effected with **3** (10 mol%) and *i*PrOH (10 equiv, distilled from CaH_2) in freshly distilled CH_2Cl_2 (0.2 M) under the indicated reaction conditions. [b] The reaction was carried out in reagent grade CH_2Cl_2 (1.0 M) and distilled *i*PrOH (10 equiv) in the presence of **3** (5 mol%), prepared from $Al(OiPr)_3$ and **2**, under the given conditions. [c] Yield of isolated product. [d] The *cis*/*trans* ratio was 17:83.

To gain information about the actual structure of the new aluminum catalyst, we prepared the complex of the catalyst precursor **4** with DMF as a model example (Scheme 3), and the structure was determined by single-crystal X-ray diffraction analysis, which revealed a dimeric structure with unique pentacoordinate aluminum centers (Figure 1).[11, 12] Thus, the formation of the expected seven-membered cyclic structure was unambiguously verified. Notably, the trifluoromethyl moiety was found to be located away from the aluminum center, suggesting that the introduction of the perfluoroalkyl group essentially provides an electronic effect rather than a steric one.



Scheme 3. Preparation of the model complex **4**-DMF.

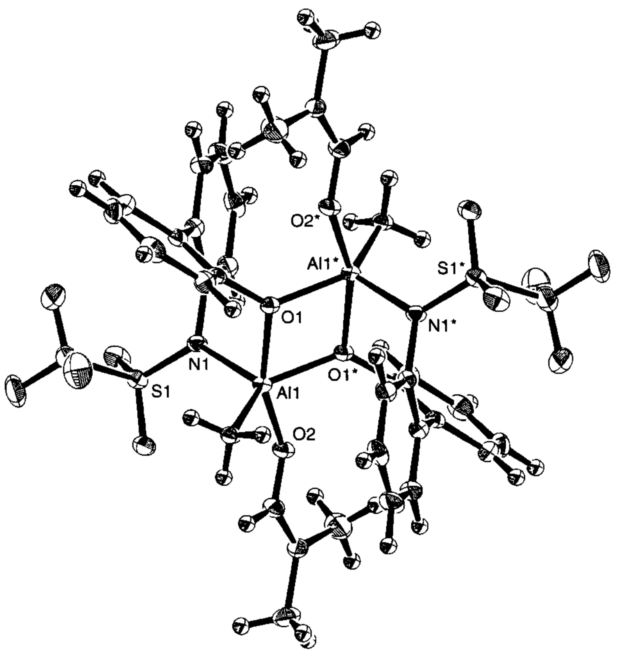


Figure 1. Structure of the **4**-DMF complex (ORTEP representation).

Based on the results, we then conducted scale-up experiments to illuminate the practical aspect of our approach, and first examined the possibility of using $Al(OiPr)_3$ as an aluminum source to avoid the rather troublesome handling of Me_3Al. Fascinatingly, simple mixing of 10 mol% each of commercially available $Al(OiPr)_3$[13] and **2** in CH_2Cl_2 at room temperature, followed by treatment with *i*PrOH (10 equiv) and acetophenone at 25 °C for 5 h resulted in the formation of *sec*-phenethyl alcohol in 82 % yield,[14, 15] indicating the intervention of extremely facile ligand exchange.[16] With this simple yet efficient process in hand, the reactions with 5 g of the starting ketones were undertaken with a lower catalyst loading (5 mol %), which scarcely affect the outcome of the catalysis. The results included in Table 2 demonstrate the potential utility of the present method.[17] Importantly, these product yields were achieved at high substrate concentration (1.0 M) with reagent grade CH_2Cl_2, which also simplifies the operations of this MPV reduction procedure.

In summary, we have devised an essentially new aluminum alkoxide that exerts high catalytic activity with *i*PrOH as a hydride donor in the MPV reduction of various ketone carbonyl groups. This is the most reactive aluminum-based catalyst reported so far and has remarkable potential for practical use. Further improvement of the reactivity and development of an asymmetric version of the reaction are currently under investigation in our laboratory.

Experimental Section

Scale-up reaction with acetophenone: 2-Hydroxy-2′-(perfluorooctanesulfonylamino)biphenyl (1.39 g, 2.1 mmol) and Al(O*i*Pr)$_3$ (0.43 g, 2.1 mmol)[13] were placed in a dry, two-neck flask with a Teflon-coated stirring bar under argon, and CH_2Cl_2 (42 mL, reagent grade purchased from Wako Chemical Co., Ltd.) was introduced. The resulting mixture was stirred for 15 min at room temperature and then 2-propanol (31.3 mL, 412 mmol) distilled from CaH_2 was introduced at the same temperature and stirring was continued for an additional 15 min. Freshly distilled acetophenone (5 g, 41.6 mmol) was added at 25 °C and the reaction solution was stirred for 5 h. This solution was poured into 1 N HCl and extracted three times with diethyl 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 ($H = 12$ cm, $\varnothing = 7$ cm, acetone/hexane = 1:9 as eluant) gave *sec*-phenethyl alcohol (4.15 g, 34.0 mmol; 82 % yield). The ligand, 2-hydroxy-2′-(perfluorooctanesulfonylamino)biphenyl, can be recovered by subsequent elution with ethyl acetate. In addition, purification of the reduction product by vacum distillation is also recommended.

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[7] For other examples, see: a) D. Barbry, S. Torchy, *Tetrahedron Lett.* **1997**, *38*, 2959; b) P. S. Kumbhar, J. Sanchez-Valente, J. Lopez, F. Figueras, *Chem. Commun.* **1998**, 535; c) R. Anwander, C. Palm, G. Gerstberger, O. Groeger, G. Engelhardt, *Chem. Commun.* **1998**, 1811; d) B.-T. Ko, C.-C. Wu, C.-C. Lin, *Organometallics* **2000**, *19*, 1864.

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[9] Attempted reduction of acetophenone with previously reported (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum)[8] (10 mol %) as a catalyst under otherwise identical conditions produced *sec*-phenethyl alcohol in 35 % yield.

[10] The requisite aluminum ligand **2** can be readily prepared from phenol in five steps: 1) NaH, methoxymethyl chloride (MOMCl), THF (99 %); 2) BuLi, ether, then B(OMe)$_3$, H_3O^+ (85 %); 3) 2-bromoaniline, Pd(OAc)$_2$, PPh_3, K_2CO_3, DME (70 %); 4) BuLi, *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine (TMEDA), $C_8F_{17}SO_2F$, diethyl ether (50 % with recovery of the starting material); 5) HCl, MeOH (99 %). Spectroscopic characterization of **2**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.92$ (s, 1 H; NH), 7.65 (dd, $J = 1.6$, 8.0 Hz, 1 H; ArH), 7.32–7.47 (m, 4 H; ArH), 7.26 (dd, $J = 1.6$, 8.0 Hz, 1 H; ArH), 7.09 (dt, $J = 1.2$, 7.6 Hz, 1 H; ArH), 6.95 (dd, $J = 1.0$, 8.2 Hz, 1 H; ArH), 5.44 (s, 1 H; OH); IR (KBr): $\tilde{\nu} = 3476$, 3194, 1489, 1440, 1408, 1356, 1269, 1232, 1213, 1205, 1182, 1155, 1065, 935, 835, 752 cm^{-1}; MS: *m/z* (%): 667 [M^+], 184 (100), 156, 154; HRMS calcd for $C_{20}H_{10}F_{17}NO_3S$: 667.0109 [M^+], found: 667.0106 [M^+]; elemental analysis calcd (%) for $C_{20}H_{10}F_{17}NO_3S$: C 36.00, H 1.51, F 48.40, N 2.10; found: C 35.71, H 1.35, F 48.32, N 2.40.

[11] Crystal structure data for the complex **4**-DMF collected at 123 K: $C_{34}H_{36}Al_2F_6N_4S_2O_8$, $M_r = 860.75$, monoclinic, space group $P2_1/c$, $a = 9.4834(7)$, $b = 9.4378(7)$, $c = 21.375(1)$ Å, $\beta = 97.856(3)°$, $V = 1895.2(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.508$ g cm^{-3}, $R_1 = 0.063$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165945. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] Shibasaki, Sasai, and co-workers have reported the structure of the pentacoordinate aluminum complex [$(CH_3)_2Al_2$(binaphthoxide)$_2$(thf)$_2$]. T. Arai, H. Sasai, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 441.

[13] Purchased from Aldrich Chemical Co., Ltd. (99.99 % purity).

[14] This simple method resulted in a slight decrease of the chemical yield probably due to the incomplete catalyst formation, which is technically inevitable at present.

[15] Attempted use of other representative metal alkoxides as catalyst under similar reaction conditions gave the following results: 58 % with Gd(O*i*Pr)$_3$; 51 % with Sm(O*i*Pr)$_3$; 0 % with Zr(OR)$_4$ (R = *i*Pr, *t*Bu).

[16] As expected, attempted reduction of acetophenone with Al(O*i*Pr)$_3$ (10 mol %) and *i*PrOH (10 equiv) in CH_2Cl_2 at 25 °C for more than 5 h showed no evidence of the product formation.

[17] For the result of the scale-up reaction with acetophenone, see Experimental Section.