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$Al(OtBu)_3$ as an Effective Catalyst for the Enhancement of Meerwein–Ponndorf–Verley (MPV) Reductions

Kyle Flack,[†,§] Kristen Kitagawa,[†,§] Pamela Pollet,[†,§] Charles A. Eckert,[†,‡,§] Kent Richman,[⊥] Joy Stringer,[⊥] William Dubay,[⊥] and Charles L. Liotta*[,†,‡,§]

[†]School of Chemistry and Biochemistry, and [‡]School of Chemical and Biomolecular Engineering, and [§]Specialty Separation Center, Georgia Institute of Technology, Atlanta, Georgia

[⊥]American Pacific Corporation - Fine Chemicals (AMPAC), Rancho Cordova, California

ABSTRACT: The Meerwein–Ponndorf–Verley (MPV) reduction of aldehydes and ketones has been the cornerstone in many multistep syntheses. Herein we report the use of $Al(OtBu)_3$ instead of the commonly used $Al(OiPr)_3$ which results in a dramatic rate increase and significantly lower catalyst loading for the reduction of (1) model compounds benzaldehyde and acetophenone, and (2) *N*-(tert-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone or (*S*)-CMK, a key intermediate in HIV protease inhibitor synthesis.

INTRODUCTION

The reduction of aldehydes and ketones to the primary and secondary alcohols, respectively, represent important synthetic transformations. Numerous homogeneous and heterogeneous reduction systems for this specific transformation have been reported in the literature.[1] One of the most chemoselective and mild reactions for these types of reductions is the Meerwein–Ponndorf–Verley (MPV) reduction,[2] which involves the reaction of aldehydes or ketones with an aluminum alkoxide in an alcohol solvent. The workhorse reagent is aluminum isopropoxide in isopropyl alcohol. The accepted reaction mechanism[3] is shown in Figure 1. The critical step, after

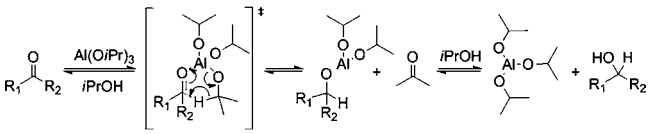

Figure 1. Mechanism of the reduction of carbonyls through reduction with $Al(OiPr)_3$ to alcohol products.

complexation of the aluminum with the carbonyl oxygen, is the hydride transfer from the α position of the isopropoxide ligand to the carbonyl carbon through a six-membered ring transition state. This then results in the formation of an aluminum adduct of the reduced carbonyl reactant as well as the oxidized alcohol reactant (most often the solvent). The transition state is shown in Figure 2.

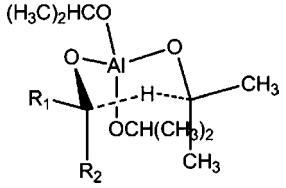

Figure 2. Six-membered transition state in the MPV reduction.

The MPV reduction is a reversible reaction (the reverse reaction is the Oppenauer oxidation[4]). Hence, the formation of the reduction products (alcohols) is favored by optimizing temperatures and using large loadings of the metal alkoxide and/or a secondary alcohol which plays the dual role of reagent and solvent. It should be pointed out that, in principle, catalytic quantities of aluminum reagent can be employed since ligand exchange can occur after hydride transfer such that another carbonyl group can coordinate with the aluminum. Unfortunately, the latter step is usually a slow process. Consequently, the aluminum alkoxide is often used in near stoichiometric quantities.

It is often the case that $Al(OiPr)_3$-catalyzed MPV reductions can take long periods of time to reach completion. As a consequence, we aimed at maximizing the rate of reaction with a highly active metal catalyst species. In fact, many catalysts[5] and conditions have been developed to enhance the MPV reduction with respect to rate and yield for the reductions of aldehydes and ketones, including bidentate aluminum reagents,[6] alkylboranes,[7,8] and lanthanide based systems.[9−11] For example, bidentate aluminum species have been successfully used to improve the reduction of benzaldehyde. However, the formation of the bidentate ligands requires in situ synthesis from reactive, highly air-sensitive trimethylaluminum. Although uncontested improvements were made to the reaction performances, practical, industrial applications remain limited by the reactive nature of alkylaluminum species such as pyrophoricity. Unless easily recyclable, their use for industrial processes could become prohibitive.

In contrast to these rather expensive reagents, the literature contains a few reports concerning the use of $Al(OtBu)_3$ in isopropyl alcohol in accelerating the rate of MPV reductions. These reports document the use of $Al(OtBu)_3$ in the MPV reduction as an aluminum catalyst to assist in the stereochemical outcome of one particular reduction.[12,13] The in situ

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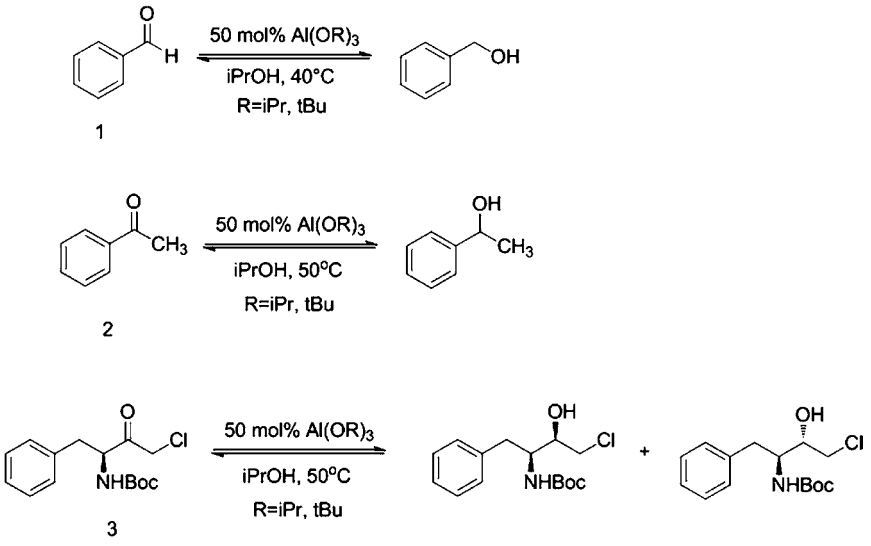

Figure 3. Model compounds investigated in the MPV reduction with $Al(OtBu)_3$ and $Al(OiPr)_3$.

formation of TFA-$Al(OtBu)_3$ adducts[14] do indeed enable the reduction of benzaldehyde at an enhanced rate compared to the conventional reduction. However, these protocols suffer from the competing aldol reactions. It is conjectured that the trifluoroacetic acid catalyzes the exchange of ligands attached to the aluminum centers. At first glance the use of $Al(OtBu)_3$ may be surprising since the *tert*-butoxide ligand has no α-hydrogens. On closer inspection, however, it is clear from the proposed mechanism that ligand exchange takes place such that a *tert*-butoxide ligand can be replaced by an isopropoxide group.

Herein, we report the use of $Al(OtBu)_3$ as a highly active, efficient, and cost-effective catalyst for MPV reductions of model compounds benzaldehyde **1**, acetophenone **2**, and *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone **3** or (*S*)-CMK, a key intermediate in HIV-protease inhibitor synthesis (shown in Figure 3).[15]

RESULTS AND DISCUSSION

$Al(OtBu)_3$: A Rate-Enhancing Catalyst. The comparative batch-mode kinetic results of the MPV reductions of benzaldehyde, acetophenone, and *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone using 50 mol % $Al(OtBu)_3$ and $Al(OiPr)_3$ in isopropyl alcohol solvent are graphically summarized in Figures 4, 5, and 6, respectively. The reactions were conducted on a 5 mL scale. Starting material concentrations of 0.166 M were used for each reaction. In all

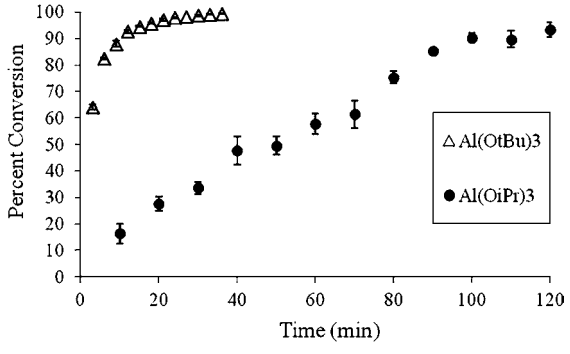

Figure 4. Comparison of the reaction progression as a function of time for the reduction of benzaldehyde with $Al(OiPr)_3$ and $Al(OtBu)_3$.

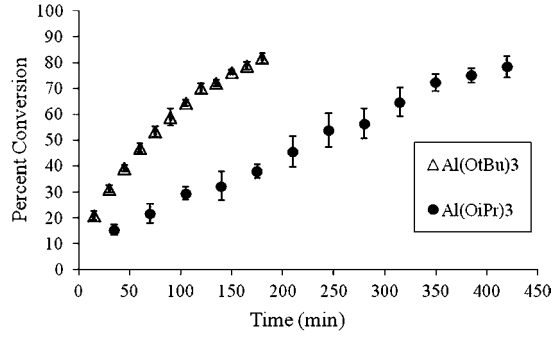

Figure 5. Comparison of the reaction progression as a function of time for the reduction of acetophenone with $Al(OiPr)_3$ and $Al(OtBu)_3$.

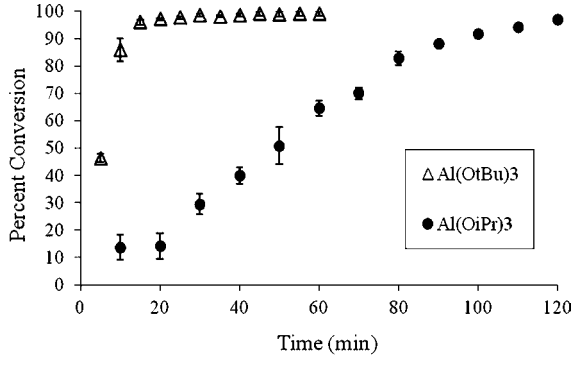

Figure 6. Comparison of the reaction progression as a function of time for the reduction of (S)-CMK with $Al(OiPr)_3$ and $Al(OtBu)_3$.

cases, the rates of reduction employing $Al(OtBu)_3$ were significantly greater than the rates using $Al(OiPr)_3$.

HPLC was employed to follow the rates of reduction for each of the carbonyl substrates. Both the conversion of the starting carbonyl substrate and the appearance of the corresponding alcohol product were monitored. A one-to-one correspondence was always observed within experimental error. In addition, no byproducts were detected; only the reduction of the carbonyl functionality was observed. The reduction of benzaldehyde, **1**, was essentially complete after about 20 min when $Al(OtBu)_3$ was employed. In contrast, only approximately

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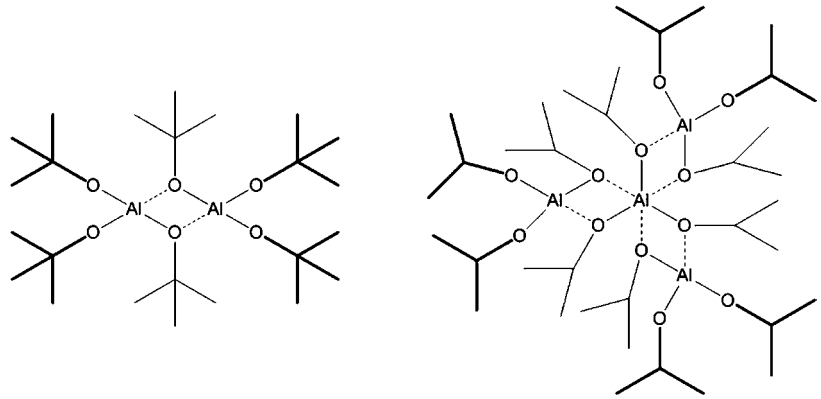

Figure 7. Structures of the dimeric $Al(OtBu)_3$ and tetrameric $Al(OiPr)_3$. (Exchangeable ligands are shown in bold.)

30% reduction took place during the same period of time with $Al(OiPr)_3$. Acetophenone, **2**, a more sterically hindered carbonyl, required approximately 3 h for 80% reduction with $Al(OtBu)_3$. The rate was substantially slower when employing $Al(OiPr)_3$; only 30% reduction took place during the same period of time. The results with *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone, **3**, were quite dramatic. Even though the substrate was a sterically hindered ketone, the reduction using the $Al(OtBu)_3$ was complete in less than 20 min. The electron-withdrawing effect of the chlorine substituent could have played a role in influencing the rate. The chlorine makes the carbonyl carbon more electrophilic, thus enhancing the hydride transfer rate. Two hours of reaction time were required using the $Al(OiPr)_3$ under the same conditions. Two important observations should be pointed out with regard to the reduction of **3**: (1) when employing 50 mol % aluminum alkoxide catalyst, the alcohol products precipitate from solution as the reaction progresses, and (2) although there is a dramatic rate difference between the two aluminum reagents, the diastereomeric ratio (*S*,*S*)/(*S*,*R*) remained unchanged at 99.4/0.6.

Aluminum Alkoxide State of Aggregation. It is interesting to speculate why the *tert*-butoxy derivative of aluminum is a much more reactive reagent than its *iso*-propoxy counterpart. It is believed that the difference in aggregation state results in the superior activity of aluminum *tert*-butoxide. In fact, in benzene, aluminum isopropoxide is known to exist as a tetramer, whereas the aluminum *tert*-butoxide is a cyclic dimer.[16] The structures of these aluminum complexes are illustrated in Figure 7. In order for reduction to occur using $Al(OtBu)_3$, exchange of *tert*-butoxy ligands with *iso*-propoxy ligands through reaction with isopropyl alcohol is paramount. It is conjectured that the bridging alkoxy groups are far less prone to exchange with the carbonyl oxygen of the aldehyde or ketone compared to the nonbridging alkoxy groups (shown in **bold**).[14]

For a given mol % of aluminum alkoxide catalyst, therefore, the ratio of nonbridging to bridging alkoxide substituent for $Al(OtBu)_3$ is twice that of the *iso*-propoxy counterpart. Thus, if it is assumed that the same states of aggregation hold for these aluminum alkoxide catalysts in isopropyl alcohol, then there would be more exchangeable ligands with the former catalyst compared to the latter. Not only does the tetrameric state of aluminum isopropoxide have a hexavalent aluminum center that cannot be accessed for coordination, but the steric hindrance of the bridging isopropoxide units are believed to contribute to the slower reductions with this conventional catalyst. This suggestion is consistent with reports in the literature where it was shown that lower aggregation states of other aluminum reagents lead to faster reductions.[17,18]

A Mixed-Solvent System for MPV Reductions. The rate enhancement effects in a mixed-solvent system were investigated. We acknowledged that in only isopropyl alcohol, this rate enhancement with $Al(OtBu)_3$ was observed; however, for the applicability of this system we chose to investigate lower loadings of *i*PrOH as well. We began by using a 9:1 volume ratio of toluene/isopropyl alcohol for each of the reductions of the three model compounds. The reductions of benzaldehyde, acetophenone, and (*S*)-CMK were conducted with 50 mol % loading of $Al(OtBu)_3$ and are graphically displayed in Figures 8−10. Unquestionably, rate enhancements were maintained

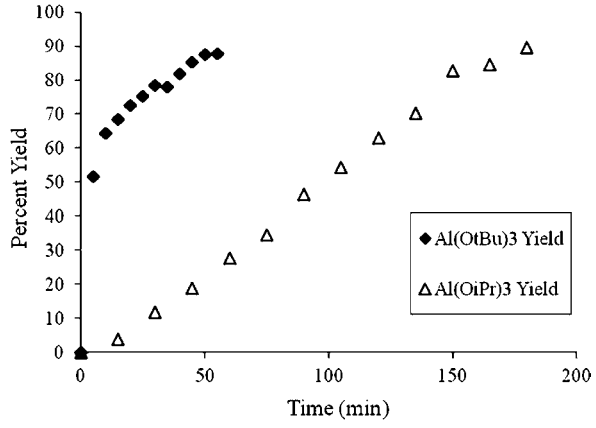

Figure 8. Reaction yield as a function of time for the MPV reduction of benzaldehyde in a solvent volume ratio of 9:1 toluene/isopropyl alcohol in batch reactors as catalyzed by 50 mol % catalyst, $Al(OiPr)_3$ or $Al(OtBu)_3$, at 40 °C.

when using $Al(OtBu)_3$. Because the concentration of isopropyl alcohol is decreased in the mixed-solvent systems, the reductions require longer periods of time to reach completion with both catalysts compared to the reductions in neat isopropyl alcohol. For example, instead of taking approximately 20 min for complete reaction of benzaldehyde, the reaction is completed in approximately one hour. Nevertheless, by judicious choice of temperatures the rates of MPV reduction in the mixed solvent system are expected to increase.

(*S*)-CMK, a Key Pharmaceutical Example. The MPV reduction of **3** is currently conducted on an industrial scale with the conventional catalyst system, $Al(OiPr)_3$, in isopropyl alcohol. Indeed, in order to facilitate the rate of this reduction,

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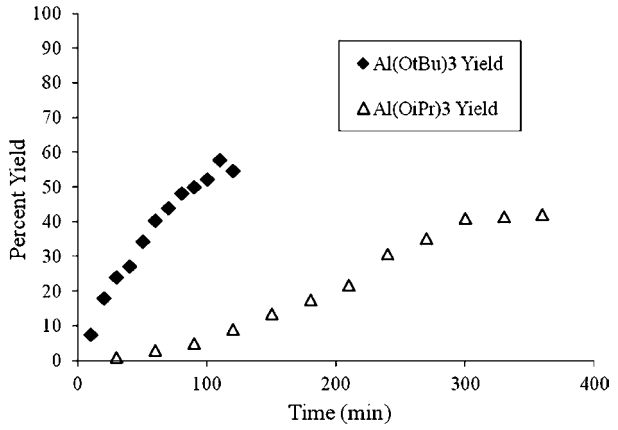

Figure 9. Reaction yield as a function of time for the MPV reduction of acetophenone in a solvent volume ratio of 9:1 toluene/isopropyl alcohol in batch reactors as catalyzed by 50 mol % catalyst, $Al(OiPr)_3$ or $Al(OtBu)_3$, at 50 °C.

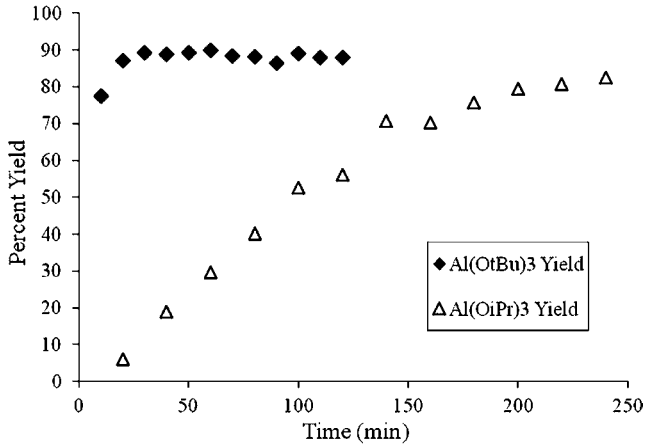

Figure 10. Reaction yield as a function of time for the MPV reduction of (S)-CMK in a solvent volume ratio of 9:1 toluene/isopropyl alcohol in batch reactors as catalyzed by 50 mol % catalyst, $Al(OiPr)_3$ or $Al(OtBu)_3$, at 50 °C.

50 mol % aluminum alkoxide reagent is employed.[19] As a consequence, large quantities of waste aluminum salts are generated in the isolation of the product. In principle, changing the ligands on the aluminum reagent from isopropoxy to *tert*-butoxy would allow the use of much smaller quantities of this reagent in order to achieve reduction within the same period of time. Of course, this would be a cost saving. In addition, the quantities of waste salt products derived from the reduction would be dramatically reduced.

Figure 11 graphically illustrates the rate profiles for the reduction of **3** as a function of $Al(OtBu)_3$ loading from 50 mol % to 5 mol % in isopropyl alcohol. The observation that the rate does not significantly change as one proceeds from 50 mol % to 20 mol % is quite surprising. It should be noted that on a small scale with 5 mol % loading, reduction failed to reach completion. This was attributed to the aluminum catalyst being quenched by inherent moisture. In contrast, on a scale 50 times larger (250 mL) with substantially larger amounts of catalyst, the 5 mol % loading results in the reaction progressing smoothly to full conversion, although at substantially slower rates than the higher catalysts loadings. In all cases the alcohol products precipitate from solution as the reaction progresses.

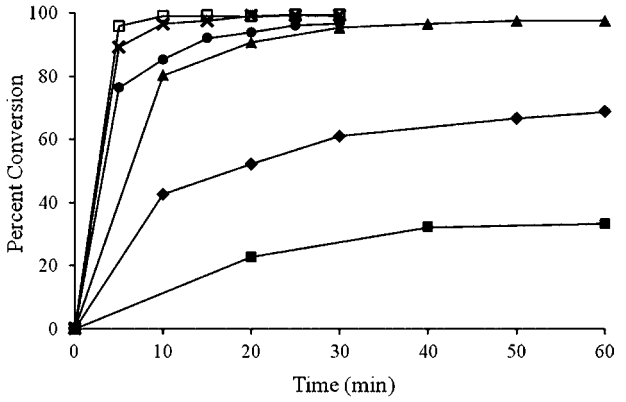

Figure 11. Conversion of (*S*)-CMK to (*S*,*S*)- and (*S*,*R*)-CMA at various $Al(OtBu)_3$ catalyst loadings in *i*PrOH. Legend: ■: 5 mol % (on a 250-mL scale), ♦: 10 mol %, ▲: 20 mol %, ●: 30 mol %, × 40 mol %, □: 50 mol %.

The use of reduced amounts of aluminum reagent provides the foundation for the development of a "greener" and more sustainable chemical process for the current reduction of (*S*)-CMK. The conventional MPV reduction of (*S*)-CMK using 50 mol % $Al(OiPr)_3$ has been successfully conducted on an industrial scale, and alcohol product precipitation does not hinder the large-scale industrial process.[19] Thus, one can envision that using much lower loadings of $Al(OtBu)_3$ (20 mol % or less) on an industrial scale would be effective at reducing (*S*)-CMK with a substantial cost savings since much smaller amounts of aluminum catalyst would be employed in the reduction process and reduced amounts of aluminum salt waste would be generated.

■ CONCLUSIONS

The MPV reaction is an important method for the reduction of aldehydes and ketones to primary and secondary alcohols, respectively. It has been demonstrated that $Al(OtBu)_3$ in isopropyl alcohol dramatically enhances the rate of reduction compared to the classical aluminum reagent $Al(OiPr)_3$. As a consequence, the amount of reagent needed could be greatly reduced. In particular, the MPV reduction process of (S)-CMK, which currently employs 50 mol % aluminum catalyst, could easily be reduced to 20 mol % or less with no significant change in the current process. The use of $Al(OtBu)_3$ would essentially be a "drop in." The net result offers a distinct advantage in time to production for larger-scale reactions and potential cost savings. As a consequence of the observed enhanced rates of reduction using $Al(OtBu)_3$ we have also considered the transfer of our batch reactions results to continuous flow systems.

■ EXPERIMENTAL SECTION

Methods and Materials. All anhydrous solvents were directly purchased from Sigma Aldrich. Acetophenone and benzaldehyde were distilled under vacuum following literature methods.[20] All other chemicals were purchased from Sigma Aldrich and used as received.

Reactions. The reactions were run in a Brinkmann 12-reaction carousel apparatus equipped with a heating and reflux block, integrated temperature controller, and simultaneous stirring of all 12 glass reaction vessels. The total volume of each reaction was 5 mL. This apparatus allowed for excellent control temperature, mixing, and reaction under an inert atmosphere.

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All solutions and reagents were prepared under anhydrous conditions.

(*S*)-CMK Reduction. (*S*)-CMK (0.475 g, 1.59 mmol) was added to a carousel tube and placed under argon atmosphere. Five milliliters of anhydrous *i*PrOH was added, and the mixture was brought to 50 °C. After the temperature had equilibrated at this temperature, $Al(OiPr)_3$ (0.170 g, 0.83 mmol) or $Al(OtBu)_3$ (0.205 g, 0.83 mmol) was added through the inlet port of the carousel tube to begin the reaction. After the allotted reaction time, the tube was removed from the carousel and placed in an ice bath. Two milliliters of 2 M HCl was then added to quench the reaction, and the reaction mixture was then diluted with MeOH to achieve homogeneity (either 20 or 30 mL). A 0.25 or 0.35 mL aliquot, depending on dilution (27 or 37 mL total reaction solution), was taken and diluted to 1 mL with MeOH in a GC Vial. The sample was analyzed by HPLC. Samples were taken every 10 min. Reaction samples were quenched every 10 min when $Al(OiPr)_3$ was used as the catalyst and every 5 min when $Al(OtBu)_3$ was used.

Benzaldehyde Reduction. $Al(OiPr)_3$ (0.170 g, 0.83 mmol) or $Al(OtBu)_3$ (0.205 g, 0.83 mmol) was added to a carousel tube and placed under argon atmosphere. Five milliliters of anhydrous *i*PrOH was added, and the mixture was brought to 40 °C. After the solution had equilibrated at this temperature, freshly distilled benzaldehyde (165 μL, 1.59 mmol) was syringed through the inlet port of the carousel tube to initiate the reaction. After the allotted reaction time, the tube was removed from the carousel and placed in an ice bath. Two milliliters of 2 M HCl was added to quench the reaction, the reaction mixture was then diluted with 10 mL MeOH, and a 0.15 mL aliquot was taken from the reaction solution and diluted with 0.85 mL of MeOH in a GC Vial. The sample was analyzed by HPLC. Reaction samples were quenched every 10 min when $Al(OiPr)_3$ was used as the catalyst and every 3 min when $Al(OtBu)_3$ was used.

Acetophenone Reduction. $Al(OiPr)_3$ (0.170 g, 0.83 mmol) or $Al(OtBu)_3$ (0.205 g, 0.83 mmol) was added to a carousel tube and placed under inert atmosphere. Five milliliters of anhydrous *i*PrOH was added and the mixture was brought to 50 °C. After the solution had equilibrated at this temperature, freshly distilled acetophenone (190 μL, 1.59 mmol) was syringed through the inlet port of the carousel tube to begin the reaction. After the allotted reaction time, the tube was removed from the carousel and placed in an ice bath. Two milliliters of 2 M HCl was added to quench the reaction, the reaction mixture was then diluted with 10 mL of MeOH, and a 0.15 mL aliquot was taken from the reaction solution and diluted with 0.85 mL of MeOH in a GC Vial. The sample was analyzed by HPLC. Reaction samples were quenched every 35 min when $Al(OiPr)_3$ was used as the catalyst and every 15 min when $Al(OtBu)_3$ was used.

MPV Reductions in Toluene/*i*PrOH (9:1). The same reaction conditions and experimental methods were used as described in the previous carousel reactions with 4.5 mL of anhydrous toluene and 0.5 mL of *i*PrOH instead of 5 mL of *i*PrOH. The workup procedure was the same for each substrate investigated. The reaction quench times for benzaldehyde in the mixed-solvent system using $Al(OiPr)_3$ as the catalyst was every 15 min and every 5 min when $Al(OtBu)_3$ was used. For acetophenone the quench times were every 30 min when using $Al(OiPr)_3$ and every 10 min when using $Al(OtBu)_3$. For the reduction of (S)-CMK with mixed solvent, the quench interval was every 20 min when using $Al(OiPr)_3$ and every 10 min when using $Al(OtBu)_3$.

(*S*)-CMK Reduction at Varying Catalyst Loadings (Carousel). For the reduction of (*S*)-CMK at varying catalyst loadings, the general procedure is as follows: (*S*)-CMK (0.475 g, 1.59 mmol) was added to a carousel tube and purged with nitrogen. Five milliliters of anhydrous *i*PrOH was then added, and the solution was brought to 50 °C. To start the reactions, $Al(OtBu)_3$ (50 mol % (0.205 g), 40 mol % (0.164 g), 30 mol % (0.123 g), 20 mol % (82.0 mg), 10 mol % (41.0 mg), 5 mol % (20.5 mg)) was added through the inlet port at the top of the tube, subsequently quenched with 2 mL of 2 M HCl in an ice bath, and finally diluted with MeOH until achieving homogeneity. Samples were then analyzed following the HPLC method described below. Quench times for each catalyst loading were as follows: 50, 40, and 30 mol % were every 5 min; 20, and 10 mol % were every 10 min; and 5 mol % was every 20 min.

(*S*)-CMK Reduction at 5 mol % Catalyst Loading Scale-Up (Batch). In a 500 mL stirred RB flask under nitrogen, (*S*)-CMK (23.75 g) was dissolved in 250 mL of anhydrous *i*PrOH and heated to 50 °C. When the solution reached temperature, $Al(OtBu)_3$ (0.985 g) was added and the reaction was started. One milliliter aliquots were taken every 20 min. Each aliquot was quenched with 2 M HCl (0.4 mL) and diluted with MeOH (4 mL). Then, 0.3 mL aliquots of the sample were diluted to 1 mL with MeOH, and analysis was conducted following the general HPLC method described below.

HPLC Analysis Method. Reaction samples were run on an HP 1100 series HPLC equipped with a UV detector set to λ = 210 and 254 nm, and used a Phenomenex Luna 5 μ C18(2) reverse-phase column and guard column. . An isocratic HPLC method was used, using water (0.1% TFA buffer) 52% and MeCN 48% as the mobile phases at a flow rate of 1.5 mL/min. The column temperature was set to 40 °C. Calibration curves were performed in order to determine the concentration of the compounds: benzaldehyde, acetophenone, (*S*)-CMK and their corresponding alcohols, benzyl alcohol, 1-phenylethanol, (*R*,*S*)-CMA, and (*S*,*S*)-CMA, respectively.

AUTHOR INFORMATION

Corresponding Author

*charles.liotta@chemistry.gatech.edu

Notes

The authors declare no competing financial interest.

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