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A Mechanistic Investigation of the Asymmetric Meerwein−Schmidt−Ponndorf−Verley Reduction Catalyzed by BINOL/$AlMe_3$—Structure, Kinetics, and Enantioselectivity

Christopher R. Graves, Hongying Zhou, Charlotte L. Stern, and SonBinh T. Nguyen*

Department of Chemistry and Institute for Catalysis in Energy Processes, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113

stn@northwestern.edu

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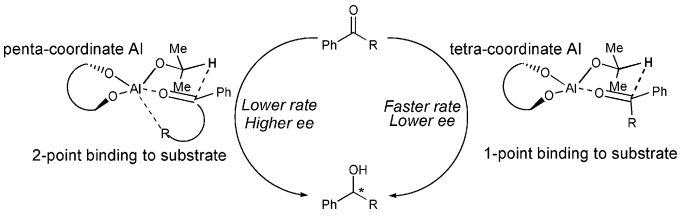

The kinetics of the Al-catalyzed asymmetric Meerwein−Schmidt−Ponndorf−Verley (MSPV) reduction are presented. Structural identification of the catalytic precursor formed in situ between (*S*)-2,2′-dihydroxy-1,1′-binapthyl ((*S*)-BINOL), $AlMe_3$, and 2-propanol was established through ^1H and ^{27}Al NMR spectroscopies, and APCIMS. All experimental evidence points toward the formation of a BINOL-chelated, pentacoordinate aluminum species in solution. Ligand-accelerated catalysis was confirmed for the phenolate/$AlMe_3$/2-propanol system. The rate law for the catalytic reaction was determined to be nearly unimolecular dependent on aluminum, zero-order dependent on substrate, and inversely dependent on 2-propanol. At the low catalyst loading employed in the BINOL/$AlMe_3$ system, the inherent reversibility of the MSPV reaction does not affect product yield or enantiomeric excess over time. Systematic ligand studies imply that while a tetrahedral geometry around the aluminum center may result in the most active MSPV reduction catalysts, the enantioselectivity of the reaction is enhanced when the aluminum center allows for a 2-point coordination of the substrate to achieve a pentacoordinate geometry with the fifth ligand weakly coordinated to the axial site of a *pseudo* square pyramid.

Introduction

The Meerwein−Schmidt−Ponndorf−Verley (MSPV) reduction of carbonyl substrates to their corresponding alcohols,[1−3] first reported in the mid 1920s, is a highly chemoselective reaction that can be performed under mild conditions. Utilizing secondary alcohols, most often 2-propanol, as benign and inexpensive hydrogen sources, the reaction is mediated by easily accessible and regenerable aluminum alkoxides.[4−6] However, despite the practical advantages of high chemoselectivity, easily removed side product, and applicability to both laboratory and large-scale synthesis, it was largely supplanted in the late 1950s by methods utilizing boro- and aluminum hydrides.[7] This is partially due to the fact that traditional MSPV protocols often required super-stoichiometric amounts of aluminum alkoxides to obtain satisfactory yields of alcohol in reasonable reaction times.[5] It was not until recent years, almost a century after its discovery, that catalytic variants of this reduction have been realized. These examples could be divided into two classes: (1) protic acid-activated aluminum alkoxides[8,9] and (2) "well-defined" aluminum complexes[10−16] where the aluminum centers are chelated by multidentate ligands.[4] Both of

* To whom correspondence should be addressed.

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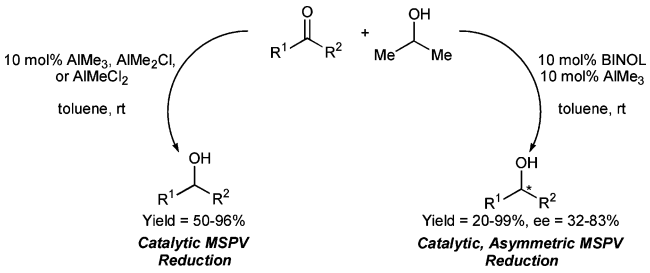
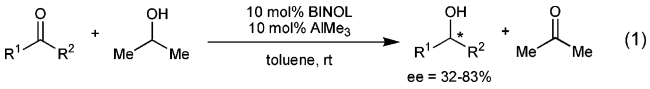
SCHEME 1. The MSPV Reduction Catalyzed by Simple Aluminum Complexes (Left) and the Asymmetric MSPV Reduction Catalyzed by BINOL/$AlMe_3$ Precatalyst Mixture (Right)



these reported methods suffered from either decreased selectivity or the use of elaborate, difficult-to-synthesize ligand frameworks. We recently demonstrated that the catalytic behavior of the MSPV reduction is highly dependent upon the aggregation state of the aluminum: while commercial $Al(O^iPr)_3$ possesses bridging alkoxides and is an inefficient catalyst, freshly prepared, largely non-aggregated aluminum alkoxides are much better, allowing for high yields of alcohols under mild reduction conditions (Scheme 1, left).[17] Furthermore, a practical catalytic asymmetric MSPV reduction of ketones was also demonstrated: using 2-propanol as the achiral hydrogen source and $AlMe_3$/enantiopure 2,2′-dihydroxy-1,1′-binapthyl (BINOL)[18] as the precatalyst mixture, good product yields, with moderate to good enantioselectivites, were obtained (Scheme 1, right).[19]

While the kinetic and mechanistic details of the classical $Al(OR)_3$-promoted MSPV reduction have been examined thoroughly,[20−24] little work has been performed regarding the Al-catalyzed variants. We recently reported a combined theoretical and experimental study aimed at elucidating the operative pathway of the hydride transfer, a key mechanistic step of the BINOL/$AlMe_3$-catalyzed MSPV reaction.[25] However, that study did not focus on ligand effects in catalysis, and experiments aimed at elucidating key ligand requirements for both rate acceleration and asymmetric induction were not carried out. Herein, we report a detailed investigation of the Al-catalyzed asymmetric MSPV reduction of ketones (eq 1) and discuss the



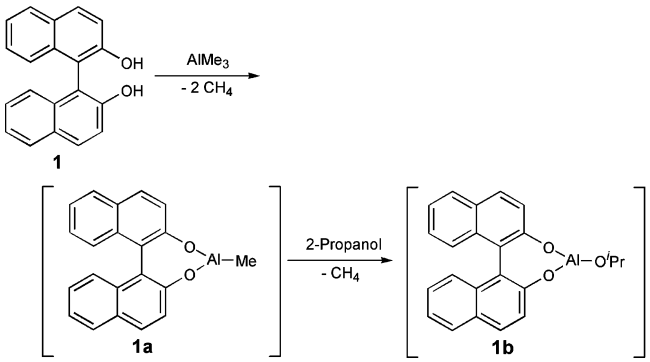
(1)

key ligand requirements for generating a successful Al-based enantioselective MSPV reduction. Specifically, we determined the reaction kinetics, the optimal aluminum coordination sphere, and the role that reversibility plays in the BINOL/$AlMe_3$-catalyzed asymmetric MSPV reduction. Notably, we suggest that the ability of α-halogenated ketone substrates to form 2-point coordination motifs with the catalyst is critical to improving the asymmetric outcome of their reduction.

Results and Discussion

Formation of the Proposed Catalytic Species. In our original communication,[19] a series of equivalency tests performed for the Al-catalyzed asymmetric MSPV reduction established the optimal ligand/metal ratio between BINOL (**1**) and $AlMe_3$ to be 1:1. Although somewhat speculative, this set of experiments led to the proposal that the active catalytic species formed in situ between BINOL and $AlMe_3$ proceeds through the initial deprotonation of the alcohols by two of the basic Al−Me moieties, thereby eliminating 2 equiv of methane to form (BINOLate)Al(Me) (**1a**). Upon the addition of 2-propanol, a third deprotonation occurs to yield (BINOLate)Al(O^iPr) (**1b**) as the active monomeric catalytic species (Scheme 2).

SCHEME 2. Proposed Formation of the Catalytic Precursor 1a and the Proposed Active Catalytic Species 1b in the Reaction of BINOL with $AlMe_3$ and 2-Propanol



Newly acquired support for the formation of a species similar to **1a** comes from titration. The ^{1}H NMR spectrum of a 1:1 mixture of **1** and $AlMe_3$ in THF-d_8 exhibits a 4:1 integration ratio for the aromatics:AlMe protons and no OH signal, suggesting a complete deprotonation.[26] In an attempt to obtain a crystal structure of **1a**, equivalent portions of trimethylaluminum and (*S*)-BINOL were reacted together in dry THF under N_2. However, isolation of the crystalline product and subsequent X-ray analysis yielded a dimeric aluminum structure, (*S*)-**2** (Figure 1 and Table 1).[27]

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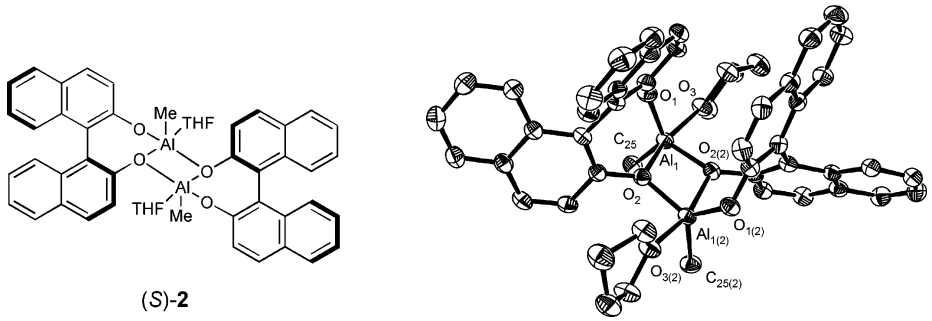
(26) The ^{1}H NMR spectrum of a 1:1 mixture of (*S*)-BINOL and $AlMe_3$ in THF-d_8 displayed the following resonances: 7.92 (broad, 3H, naphthyl), 7.32−6.85 (broad, 8H, naphthyl), 5.81 (broad, 1H, naphthyl), −0.76 (s, 3H, $AlCH_3$).

(27) This dimeric aluminum complex is similar in bonding structure to those reported by the Lin group (see refs 15 and 16).



(*S*)-**2**

FIGURE 1. An ORTEP depiction of the crystal structure of the isolated aluminum dimer (*S*)-**2** showing the atom labeling scheme and the asymmetric subunit. Thermal ellipsoids are drawn at 50% probability. Hydrogens are omitted for clarity.

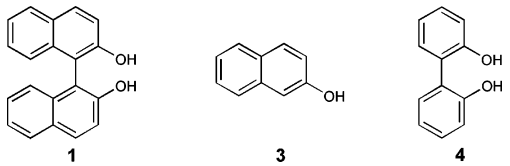
TABLE 1. Selected Bond Lengths (Å) and Angles (deg) for (*S*)-2

bonding atoms	bond length (Å)	bond angle (deg)
Al_1-O_1	1.7549(14)	
Al_1-O_2	1.9794(14)	
Al_1-O_3	1.9755(13)	
$Al_1-O_{2(2)}$	1.8249(13)	
Al_1-C_{25}	1.961(2)	
$O_1-Al_1-O_2$		90.63(6)
$O_1-Al_1-O_3$		89.73(6)
$O_1-Al_1-O_{2(2)}$		121.04(7)
$O_2-Al_1-O_{2(2)}$		74.50(6)
$O_3-Al_1-O_{2(2)}$		90.43(6)
$C_{25}-Al_1-O_1$		122.00(9)
$C_{25}-Al_1-O_2$		98.14(8)
$C_{25}-Al_1-O_3$		96.43(8)
$C_{25}-Al_1-O_{2(2)}$		116.53(8)
$Al_1-O_2-Al_{1(2)}$		104.37(6)

We hypothesized that the dimeric form of (*S*)-**2** is the energetically favored solid-state structure and that under the conditions employed for the asymmetric MSPV reduction, the dimer would break apart into the active monomeric species (*S*)-**1b**, as has been shown to occur for similar aluminum species.[16] The ^{1}H NMR spectrum of the (*S*)-BINOL/$AlMe_3$ mixture in CD_2Cl_2 showed a complete disappearance of the Al−Me signal upon the addition of 2-propanol and a growing in of the isopropoxide group, as was expected for (*S*)-**1b**. An equivalent experiment performed with dimer (*S*)-**2** in CD_2Cl_2 showed analogous results, suggesting that the last demethylation step for the dimer also occurs smoothly to give a species whose NMR spectrum is identical with that for the (*S*)-BINOL/$AlMe_3$/2-propanol mixture. The ^{27}Al NMR spectra for both aforementioned reactions also support this hypothesis. For the reaction between the (*S*)-BINOL/$AlMe_3$ mixture and 2-propanol in CD_2Cl_2, a single, broad signal at 28 ppm was detected in its ^{27}Al NMR spectrum. Similarly, the ^{27}Al NMR spectrum of a solution of (*S*)-**2** and 2-propanol in CD_2Cl_2 exhibited a single, broad signal at 30 ppm. As ^{27}Al NMR resonances in the mid-20−50 ppm range are indicative of pentacoordinate aluminum alkoxides,[28−30] the aforementioned data imply that similar pentacoordinate aluminum centers are present under both reaction conditions, presumably **1b**·2(HO^{i}Pr), where 2 equiv of 2-propanol are loosely bound to the Al center in the putative (BINOLate)Al(O^{i}Pr) intermediate **1b**.[31]

Additional support for the in situ formation of (*S*)-**1b** from both the (*S*)-BINOL/$AlMe_3$ mixture and (*S*)-**2** comes from mass spectral studies. In CH_2Cl_2, the (*S*)-BINOL/$AlMe_3$ mixture was treated with excess 2-propanol followed by direct analysis of the solution via atmospheric pressure chemical ionization mass spectroscopy (APCIMS). A clean parent ion at *m*/*z* 370.8 was detected with an isotopic pattern similar to the simulated pattern for $C_{23}H_{19}AlO_3$, the calculated molecular weight of (BINOLate)Al(O^{i}Pr) (see the Supporting Information). Direct mass spectrometric analysis of the reaction mixture between (*S*)-**2** and 2-propanol in CH_2Cl_2 also showed a clean parent ion corresponding to the molecular weight of $C_{23}H_{19}AlO_3$, with a similar isotopic pattern (see the Supporting Information). Presumably the 2 equiv of 2-propanol that are loosely bound to the Al center in the putative **1b**·2(HO^{i}Pr) solvated intermediate were lost upon ionization and only the (BINOLate)Al(O^{i}Pr) core remains. These results support our original model for catalyst formation (Scheme 2), and suggest that the Al center has two additional coordination sites available for bonding.

Ligand-Accelerated Catalysis. While the chelation environment posed by the BINOL framework around Al centers has been shown to significantly influence our asymmetric MSPV reduction, further effects of phenoxide-based ligands in the Al-catalyzed MSPV have not yet been elucidated. The initial rates[32] of MSPV reduction of acetophenone with 2-propanol were determined by using the in situ-formed BINOL/$AlMe_3$ complex, in situ-formed 2-naphthol (**3**, 2 equiv)/$AlMe_3$ complex, in situ-formed 2,2′-biphenol (BIPHEN, **4**)/$AlMe_3$ complex, and $AlMe_3$



1 **3** **4**

FIGURE 2. Phenolic compounds employed as ligands in the Al-catalyzed MSPV reduction of ketones.

alone as catalytic precursors (Figure 3). Acetophenone was reduced to *sec*-phenethyl alcohol in the presence of BINOL/$AlMe_3$ (Figure 3, B) at a rate that is approximately twice as fast as that observed for $AlMe_3$ (Figure 3, C). The analogous MSPV reduction with the (2-naphthol)$_2$/$AlMe_3$ and BIPHEN/$AlMe_3$ mixtures as catalyst precursors proceeded at rates that

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(31) While the (*S*)-BINOL/$AlMe_3$/2-propanol mixture and (*S*)-**2**/2-propanol mixtures have slightly different ^{27}Al resonances (28 and 30 ppm, respectively), this difference is not significant given the inherent broadness of the ^{27}Al NMR signals.[28,29]

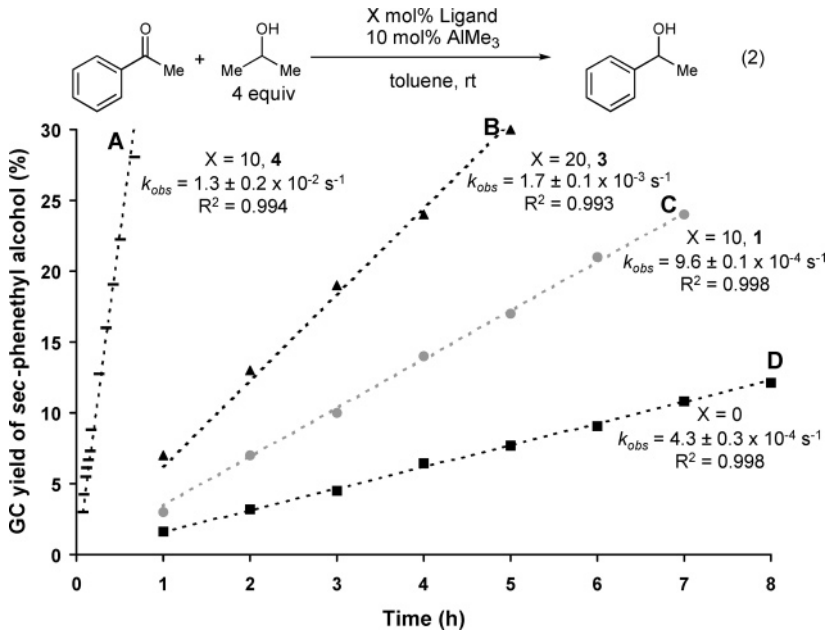

FIGURE 3. Initial rates of reaction for the MSPV reduction of acetophenone with 2-propanol, using BIPHEN/$AlMe_3$ (1:1, A), 2-naphthol/$AlMe_3$ (2:1, B), BINOL/$AlMe_3$ (1:1, C), and $AlMe_3$ (D) as the catalytic precursors.

TABLE 2. Characterization Data for the in Situ-Generated Complexes between Ligands, $AlMe_3$, and 2-Propanol

entry	ratio	proposed solution structure and ^{27}Al NMR signal	proposed gas-phase structure and calcd mol wt	APCIMS results (*m*/*z*)
1	**1**/$AlMe_3$/HO^{i}Pr (1:1:40)	(BINOLate)Al(O^{i}Pr)(HO^{i}Pr)$_2$, 28 ppm	(BINOLate)Al(O^{i}Pr), $C_{23}H_{19}AlO_3$, 370.38 g/mol	370.8
2	**3**/$AlMe_3$/HO^{i}Pr (2:1:40)	(naphtholate)$_2$Al(O^{i}Pr)(HO^{i}Pr)$_2$, 24 ppm	(naphtholate)$_2$Al(O^{i}Pr), $C_{23}H_{21}AlO_3$, 372.38 g/mol	372.9
3	**4**/$AlMe_3$/HO^{i}Pr (1:1:40)	(BIPHENate)Al(O^{i}Pr)(HO^{i}Pr)$_2$, 31 ppm	(BIPHENate)Al(O^{i}Pr), $C_{15}H_{15}AlO_3$, 270.26 g/mol	270.1

are 4 times and *30* times faster, respectively, than that observed for $AlMe_3$ (Figure 3, A and B). This observed ligand-accelerated[33] catalytic behavior suggests that phenolate ligands can greatly influence the catalytic activity of aluminum alkoxides in the MSPV reduction via both electronic and chelation effects. Not only that decreasing the electron density around the aluminum center with phenoxide ligands increases its reactivity toward MSPV reduction, constraining the ligand environment also increases its activity.

To verify that the observed rate differences shown in Figure 3 were indeed results of the different ligand environments and not simply due to differences in aluminum coordination mode, we turned to ^{27}Al NMR spectroscopy. Solutions of [2-naphthol (2 equiv) + $AlMe_3$ + 2-propanol (40 equiv)] and [BIPHEN + $AlMe_3$ + 2-propanol (40 equiv)] in CD_2Cl_2, similar to the conditions employed in the BINOL/$AlMe_3$/2-propanol MSPV reduction chemistry, were prepared and analyzed directly via ^{27}Al NMR spectroscopy (Table 2, entries 2 and 3, respectively). That the solutions exhibited signals in their ^{27}Al NMR spectra at ~30 ppm, and that these results are equivalent to those observed for the BINOL/$AlMe_3$/2-propanol combination, supports the generation of analogous pentacoordinate aluminum species[28,30] in all three cases, each of which is presumably coordinated by 2 equiv of 2-propanol in addition to three alkoxide/aryloxide ligands.

Additional support for similar Al coordination environments in all three of the aforementioned cases came from mass spectral studies. In CH_2Cl_2, the 2-naphthol/$AlMe_3$/2-propanol mixture exhibited a clean parent ion at *m*/*z* 372.9, as was expected for the proposed solvent-free (naphtholate)$_2$Al(O^{i}Pr) species (Table 2, entry 3). Analysis of the **4**/$AlMe_3$/2-propanol mixture in CH_2Cl_2 gave a similar result: a parent ion at *m*/*z* 270.1, the calculated molecular weight for the solvent-free (BIPHENate)Al(O^{i}Pr) species, was observed with an isotopic pattern similar to the generated pattern (Table 2, entry 3). Together with the aforementioned kinetic data, these experiments indicate that not only is the phenol/$AlMe_3$/2-propanol system ligand-accelerated, but variation in denticity (mono- versus bidentate) and steric constraints of the phenolic ligand, also have important rate consequences in the MSPV reduction.

Kinetics of the Asymmetric MSPV Reduction Catalyzed by BINOL/$AlMe_3$. Given the structure of intermediate **1b**, a reasonable empirical rate law for reaction 1 can be expressed in terms of three concentrations: aluminum catalyst, substrate, and 2-propanol (eq 3). Through a series of *pseudo* first-order kinetic studies, the order with respect to each reactant (*x*, *y*, *z*) may be isolated and subsequently determined.[34]

$$\text{rate} = \nu = k[\text{catalyst}]^x[\text{substrate}]^y[\text{2-propanol}]^z \quad (3)$$

Determination of the Order of Aluminum Catalyst: Discrimination between Monomeric and Dimeric Catalyst Activation. While it is generally accepted that the MSPV

(32) For this kinetic study, the initial rate of reaction was determined by GC analysis of aliquots taken from the reaction mixture at the appropriate time. Rate constants were determined from a plot of product yield versus time up to 20% yield.

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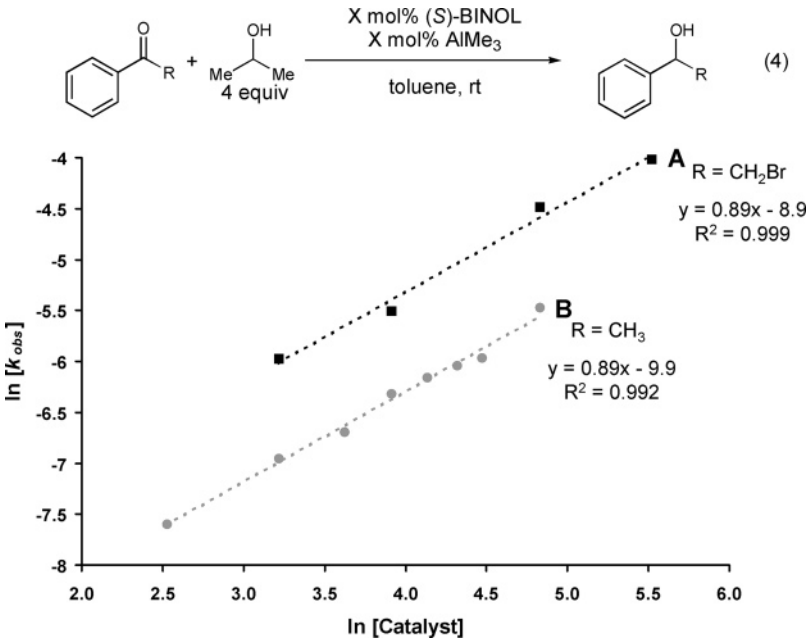


FIGURE 4. Plots of ln[k_{obs}] versus ln[catalyst] for the (BINOL)Al-catalyzed MSPV reduction of α-bromoacetophenone (R = CH_2Br, A) and acetophenone (R = CH_3, B) with 2-propanol.

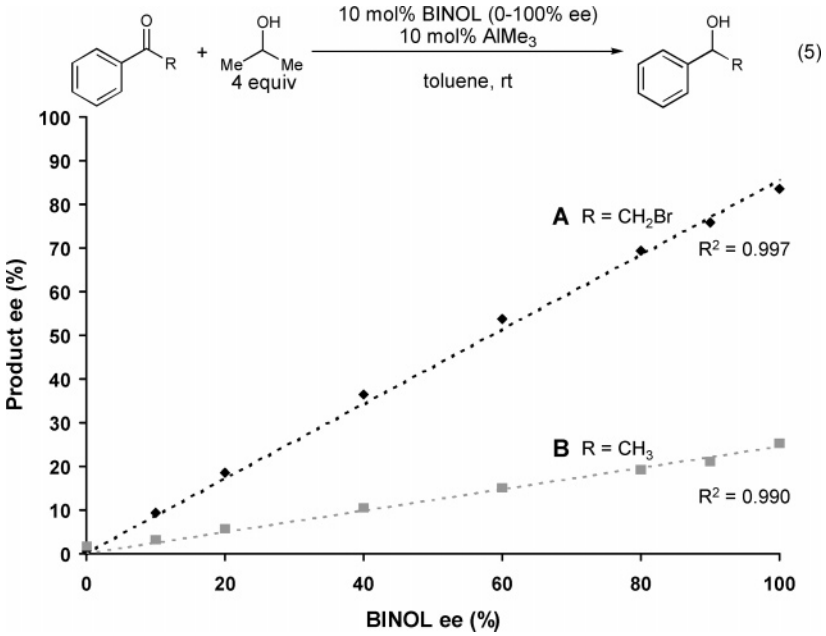


FIGURE 5. Investigation for a nonlinear effect in the BINOL/Al-catalyzed MSPV reduction of α-bromoacetophenone (A) and acetophenone (B).

reduction proceeds through a monometallic pathway in which both the carbonyl substrate and alkoxide are coordinated to a single aluminum center, recent reports suggest that substrate activation by two aluminum centers is also a viable option.[10,12] To discriminate between these two possibilities for the BINOL/$AlMe_3$ system, we first determined *x*, the catalyst order, by holding the concentration of both substrate and 2-propanol in high excess relative to catalyst. The initial rates of the (BINOL)-Al-catalyzed MSPV reduction of acetophenone and α-bromoacetophenone with 2-propanol were measured independently at various catalyst concentrations (12.5−250 mM, see Table S1 in the Supporting Information). Subsequent plots of ln[k_{obs}] versus ln[catalyst concentration] for both sets of experiments yielded catalyst orders of 0.89 (Figure 4). As orders close to 1 are most logically explained by a unimolecular dependence, it is reasonable to conclude that the (BINOLate)Al-catalyzed MSPV reduction proceeds through a monometallic catalytic intermediate.

For a number of asymmetric catalytic reactions where two chiral metal centers act cooperatively, a linear variation of the catalyst enantiopurity can result in a nonlinear variation in the enantiopurity of the product.[35] To this end, a series of MSPV reductions of α-bromoacetophenone and acetophenone were carried out independently by using the in situ-generated catalyst **1b** with varying enantiomeric purity of BINOL ligand (0−100%). The linear relationship between ligand and product ee values (Figure 5) indicates the absence of a nonlinear effect in the (BINOL)Al-catalyzed MSPV reduction, further supporting a mechanism in which two metal centers *are not* acting in concert.

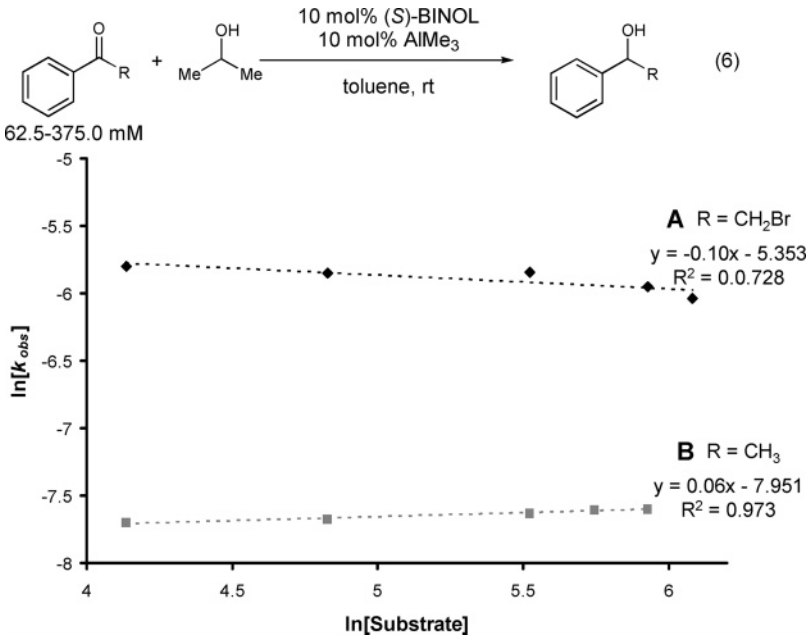


FIGURE 6. Plot of ln[k_{obs}] versus ln[substrate] for the (BINOL)Al-catalyzed MSPV reduction of α-bromoacetophenone (R = CH_2Br, A) and acetophenone (R = CH_3, B) with 2-propanol.

While we were reasonably confident at this point that the (BINOL)Al-catalyzed MSPV reduction proceeds at a single metal center, isolation of the dimeric species (*S*)-**2** provided an opportunity to investigate whether such a species can act as a possible MSPV catalyst. In the presence of DMSO, dimer (*S*)-**2** can be broken into a monomeric ((*S*)-BINOL)AlMe(DMSO) complex, similar to that observed by the Lin group for their [(μ-MMPEP)AlMe]$_2$ dimer (MMPEP = 2,2-methylenebis(4,6-di(1-methyl-1-phenylethyl)phenolate).[15] Both (*S*)-**2** and ((*S*)-BINOL)AlMe(DMSO) can catalyze the reduction of α-bromoacetophenone by 2-propanol and the product ee values in both cases were determined to be 79% in the *S* configuration, the same as that found with the in situ-generated catalyst (*S*)-**1b**.[19] That the reduction with dimer (*S*)-**2** and ((*S*)-BINOL)-AlMe(DMSO) gave results analogous to the reduction with the in situ-formed catalyst (*S*)-**1b** further supports formation of identical aluminum species for all cases under typical (BINOLate)Al-catalyzed MSPV reaction conditions. Together with the aforementioned kinetics, NMR, and MS studies, these results lend credence toward the breakdown of dimer (*S*)-**2** into the active *monomeric* catalytic species (*S*)-**1b** under MSPV reaction conditions.

Determination of Reaction Order with Respect to Substrate and 2-Propanol. Convinced that the BINOL/$AlMe_3$-catalyzed asymmetric MSPV reduction was proceeding through a monometallic mechanism, we set out to determine the reaction order with respect to both the ketone substrate and 2-propanol reductant. At a constant catalyst loading and an excess of 2-propanol, the initial rates of reduction for acetophenone and α-bromoacetophenone were determined at various substrate concentrations (62.5−375.5 mM, see Table S2 in the Supporting Information). Surprisingly, over this concentration range there was very little change[36] in reaction rate with increasing substrate concentration, as is further depicted in a plot of the ln[k_{obs}] versus ln[substrate] (Figure 6), indicating that the reaction rate is *independent* of substrate concentration.

Intrigued by these results, we investigated the rate dependence of 2-propanol. Holding the substrate concentration in high excess and using a constant catalyst loading, the initial reduction rates were determined at various 2-propanol concentrations (62.5−437.5 mM, see Table S3 in the Supporting Information). A subsequent plot of the ln[k_{obs}] versus ln[2-propanol] was generated (Figure 7), both of which indicate an inverse dependence on 2-propanol concentration.

This inverse dependence on 2-propanol can be explained via the equilibrium depicted in Scheme 3. As suggested by the aforementioned ^{27}Al NMR experiments, the maximum coordination number that the aluminum center can obtain under the (BINOLate)Al-catalyzed MSPV reaction conditions is five. Once the active catalytic species **1b** is formed, excess 2-propanol can bind to vacant coordination sites on the aluminum center, giving the tetracoordinate intermediate (**1b**·(HO^{i}Pr)); further coordination by 2-propanol would give the saturated, pentacoordinate species (**1b**·2(HO^{i}Pr)). As the aluminum center in **1b**·2(HO^{i}Pr) is fully saturated, there are no sites available for substrate to coordinate and the MSPV pathway shuts down. At increasing concentrations of 2-propanol, the equilibrium depicted in Scheme 3 shifts to the right and the inactive aluminum species becomes more prevalent, decreasing the observed reduction rate.

The above outlined equilibrium also helps explain the ca. zeroth-order rate dependence on substrate. At the large 2-propanol concentration employed in the *pseudo* first-order kinetic conditions used to determine substrate order, one would expect the major aluminum species in solution to be the MSPV-inactive **1b**·2(HO^{i}Pr). This equilibrium condition suggests that once acetophenone displaces the excess 2-propanol, reduction is rapid. At the high 2-propanol concentrations relative to substrate for all of the reactions used in this study, one would not expect to observe a major rate difference over this concentration range.

(35) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons, Inc.: New York, 1994; p 1267.

(36) The slight deviation from linearity observed at higher substrate concentrations is presumably due to reaction conditions that are no longer strictly *pseudo* first-order (ca. only 6-fold excess of 2-propanol).

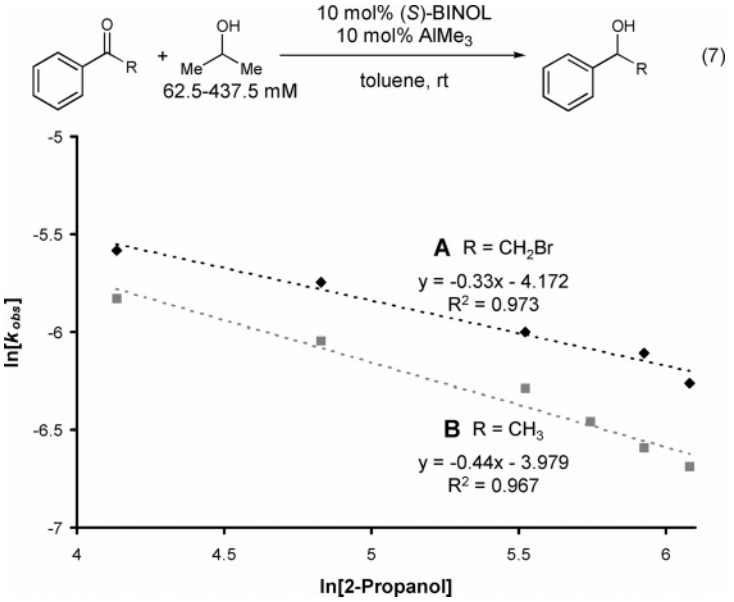


FIGURE 7. Plot of $\ln[k_{obs}]$ versus ln[2-propanol] for the (BINOL)Al-catalyzed MSPV reduction of α-bromoacetophenone (R = CH_2Br, A) and acetophenone (R = CH_3, B) with 2-propanol.

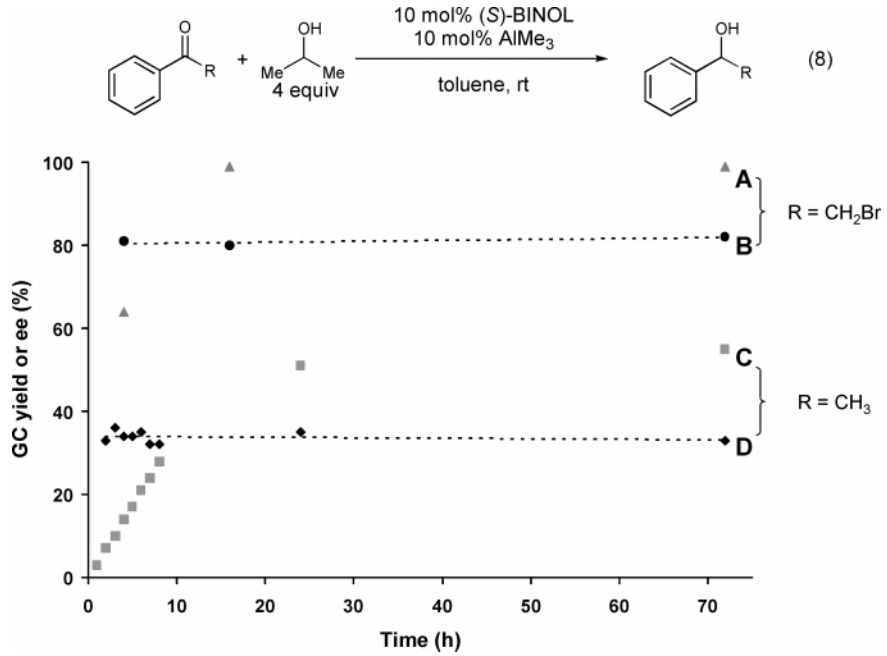
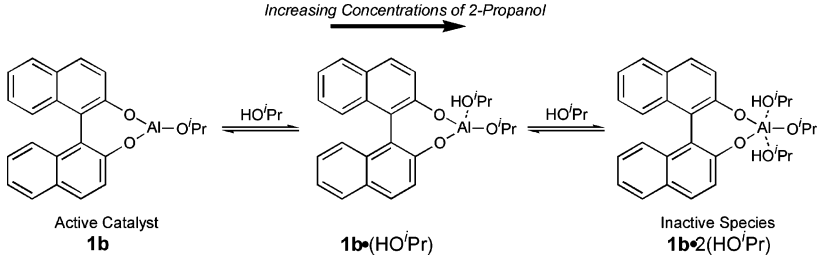


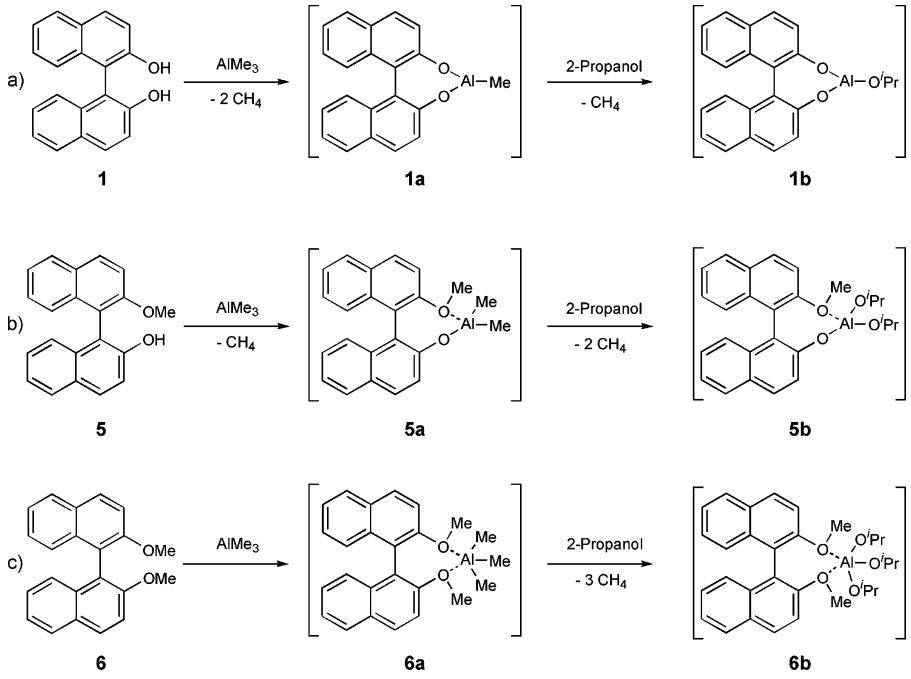
FIGURE 8. Reaction yield (▲ and ■, grey) and product ee (● and ◆) as a function of time for the MSPV reduction of α-bromoacetophenone (R = CH_2Br; yield line A (▲); ee line B (●)) and acetophenone (R = CH_3; yield line C (■); ee line D (◆)) catalyzed by (*S*)-BINOL/$AlMe_3$.

SCHEME 3. Proposed Equilibrium between the Active Aluminum Alkoxide Catalyst 1b and Excess 2-Propanol



Reversibility in the Asymmetric BINOL/$AlMe_3$-Catalyzed MSPV Reduction. Given the inherent reversibility[4,6,37] of the MSPV reduction, a successful asymmetric variant of this reaction must effectively overcome the potential for product racemization through the reversible transfer hydrogenation processes. While use of excess 2-propanol should shift equi-

SCHEME 4. Proposed Formation of the Catalytic Precursors 1a, 5a, and 6a and the Proposed Precatalysts 1b, 5b, and 6b Formed between the Reaction of $AlMe_3$ with (a) BINOL, (b) Monoether-BINOL, and (c) Diether-BINOL, Respectively, in the Presence of 2-propanol



librium toward product, the potential for reaction reversibility, especially with the build-up of reaction products, may lead to a decrease in enantiomeric excess of product over time. To verify that this was not occurring in the BINOL/$AlMe_3$ system, the reduction of α-bromoacetophenone catalyzed by in situ-formed (*S*)-**1b** with a 4-fold excess of 2-propanol was carried out and monitored over time (Figure 8, A and B). The enantiomeric purity of product remained unchanged (81 ± 2%) after 3 days (72 h). Similarly, the reduction of acetophenone, which is at a lower oxidation potential than α-bromoacetophenone,[38−40] is not debilitated by reversibility (Figure 8, C and D). The enantiomeric excess of reduction product remained at ∼35% throughout the reduction and over time, indicating that reversibility, if present, does not influence the asymmetric outcome of the ((*S*)-BINOL)Al-catalyzed MSPV reduction under experimental conditions employed for acetophenone-type substrates.

Effect of Ligand Coordinating Ability in the Asymmetric MSPV Reduction. Having established the importance of bischelating phenol-based ligands in enhancing the activity of the Al-catalyzed MSPV reduction, we compare the binding mode of **1** to the Al center with two other BINOL derivatives: **5**[41] has one phenol moiety paired with a phenol ether, while **6**[42] has both of its phenol functionalities masked as ethers (Scheme 4). Given our proposal for catalyst formation between BINOL, $AlMe_3$, and 2-propanol (vide supra), reaction of **5** and **6** with $AlMe_3$ and 2-propanol should result in aluminum intermediates that exhibit different coordination environments under typical (BINOLate)Al-catalyzed MSPV reaction conditions. Initial reaction between $AlMe_3$ and **5** would release 1 equiv of methane to afford the mono-alkoxide **5a**, which yields **5b** as a putative tetracoordinate precatalyst upon addition of excess 2-propanol (Scheme 4b). The formation of **6b** from **6** follows a similar pathway, except that the addition of $AlMe_3$ to a solution of **6** should not expel methane; rather, it would lead to dative coordination of the ligand to give the pentacoordinate metal species **6a**, which exhibits three Al−Me functionalities. Upon addition of 2-propanol, these basic moieties would be protonated to form the pentacoordinate aluminum alkoxide **6b** (Scheme 4c).

We previously reported that the combination of $AlMe_3$ with enantiomerically pure ligands (*S*)-**5** and (*S*)-**6** produced inferior catalysts (relative to the parent BINOL/$AlMe_3$ system) for the MSPV reduction of α-bromoacetophenone with 2-propanol, in both yield and selectivity.[19] Given the varying coordination environments proposed in Scheme 4 for the in situ-generated catalytic species **1b**, **5b**, and **6b**, we originally proposed three different intermediates for hydrogen transfer (tetra-, penta-, and hexacoordinate, Scheme 5, parts a, b, and c, respectively). On the basis of these models, we inferred that any Al-based MSPV catalyst that does not employ a tetrahedral geometry at the point for hydrogen transfer would lead to a decreased enantioselectivity.[43] That suggestion is now invalidated by newly acquired characterization data indicating a pentacoordinate catalytic species that exists in solution for the BINOL/$AlMe_3$/2-propanol mixture (vide supra).

(37) For recent examples of Oppenauer oxidation protocols see: (a) Ooi, T.; Otsuka, H.; Miura, T.; Ichikawa, H.; Maruoka, K. *Org. Lett.* **2002**, *4*, 2669−2672. (b) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc*. **2006**, *128*, 12596−12597.

(38) Adkins, H.; Cox, F. W. *J. Am. Chem. Soc.* **1938**, *60*, 1151−1159.

(39) Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc*. **1949**, *71*, 3622−3629.

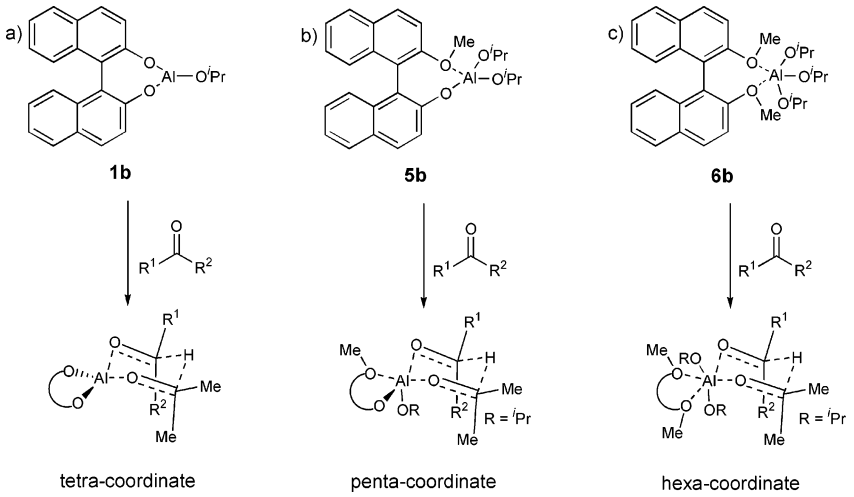
(40) Cox, F. W.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 3364−3370.

(41) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319−6337.

(42) Takahashi, M.; Ogasawara, K. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3125−3130.

(43) We originally proposed that a tetracoordinate intermediate was operative for the BINOL/$AlMe_3$/2-propanol system. On the basis of data showing reduced ee,[19] we suggested a pentacoordinate intermediate for the MSPV reduction employing the **5**/$AlMe_3$/2-propanol combination and a hexacoordinate intermediate for the **6**/$AlMe_3$/2-propanol combination, and that these higher coordination intermediates resulted in inferior asymmetric catalysts.

SCHEME 5. Previously Proposed Intermediates[19] for the MSPV Reduction of Ketones with 2-Propanol Catalyzed by 1b, 5b, and 6b



In support of the hypothesis that the solvent-free species **5b** can be formed under the experimental conditions, the APCIMS spectrum of the **5**/$AlMe_3$/2-propanol mixture exhibits a clean molecular ion at *m*/*z* equal to 444.7, with a matching isotopic pattern to that generated for $C_{27}H_{29}AlO_4$. Further, the ^{27}Al NMR spectrum of this mixture exhibits a resonance signifying a pentacoordinate aluminum species (31 ppm), consistent with a structure of **5b** surrounded by one solvent molecule. While **6** is not soluble in toluene, addition of $AlMe_3$ affords solubilization of the ligand, suggesting that a ligand−metal interaction has occurred and supporting the formation of **6a**, as does the ^{27}Al spectrum of the **6**/$AlMe_3$ mixture in CD_2Cl_2, which exhibits a signal at 35 ppm indicative of a pentacoordinate aluminum center. However, upon the addition of a small amount of 2-propanol, the solution becomes immediately heterogeneous, suggesting that protonation of the Al−Me functionalities to form the corresponding alkoxides results in expulsion of the datively bound **6**, and the ligand is not a participant in the final aluminum complex.[44]

The MSPV reduction of acetophenone with 2-propanol was carried out employing the in situ-derived species formed between $AlMe_3$ and either (*S*)-**1**, (*S*)-**5**, or (*S*)-**6** (Figure 9). Together with the aforementioned characterization data, the minimal enantiomeric excess in product obtained in the (*S*)-**6**/$AlMe_3$-catalyzed reduction further supports the dissociation of the ligand from the aluminum center under the MSPV reaction conditions. Indeed, the observed rate of reduction with this ligand (Figure 9, C) was quite close to the rate observed for the unligated, $AlMe_3$-catalyzed reduction of acetophenone (Figure 3, D).

While the (*S*)-**5**/$AlMe_3$/2-propanol mixture afforded a much more active catalyst for the MSPV reduction of acetophenone than the (*S*)-BINOL/$AlMe_3$/2-propanol equivalent, product ee was substantially reduced (Figure 9, A and B, respectively). As mentioned above, we originally suggested that this decreased selectivity was a result of deviation from an optimal tetrahedral aluminum center during the hydrogen transfer process (Scheme 5a,b).[44] However, this may be an incorrect assessment: ^{27}Al NMR data for the **5**/$AlMe_3$/2-propanol combination clearly indicate a pentacoordinate aluminum center in solution, similar to that observed for the **1**/$AlMe_3$/2-propanol mixture. That similar pentacoordinate Al-environments exist for both the (*S*)-**1** and (*S*)-**5** cases implies that a tetracoordinate intermediate is not an absolute prerequisite for a stereoselective MSPV reduction, and coordination number alone does not sufficiently explain the observed asymmetric results.

A modified explanation for the decreased product ee, as well as the increased reaction rate, obtained for MSPV reductions employing the (*S*)-**5**/$AlMe_3$ mixture as a precatalyst is as follows. In solution, the etheric oxygen of (*S*)-**5** is loosely bound to the aluminum center, similar to that proposed for the (*S*)-**6** ligand (vide supra), and can easily be displaced by the large excess (40 equiv relative to catalyst) of 2-propanol employed in our MSPV reduction. This shifts the bidentate chiral framework away from the aluminum center and results in a decrease in selectivity for the system. However, because the aluminum center becomes less sterically congested while still maintaining a phenolate linkage, the rate of acetophenone reduction would increase relative to that observed for BINOL (Scheme 6). In this sense, the monoether BINOL ligand (*S*)-**5** essentially acts as a sterically congested 2-naphthol ligand (vide supra). This result also implies that enantiomerically pure, monodentate alcohols may not impart sufficient chirality upon the aluminum center, and would be inferior ligands for the asymmetric MSPV reduction.

Substitution of the BINOL Framework. Our experiments thus far suggest that weak dative ligand coordination, such as those based on ether linkages between the BINOL ligand and aluminum, are insufficient for chiral induction in the MSPV reduction, presumably due to competitive coordination by the excess 2-propanol reductant. As diprotic BINOL-derived ligands were most optimal among the phenol-based ligands that we investigated for the asymmetric MSPV reduction, we hypothesized that incorporation of alkyl groups in the 3 and 3′ positions of the BINOL framework could potentially increase the steric bulk surrounding the Al center and lead to both a tighter transition state and a more selective catalytic species.

The MOM-protected analogue of the enantiomerically pure C_1-symmetric, 3-methylated BINOL derivative (*S*)-**7** was synthesized from methoxymethoxy (MOM)-protected (*S*)-BINOL via lithiation with 1 equiv of ^{n}BuLi and subsequent trapping of

(44) Combinations of **6**/$AlMe_3$/2-propanol and $AlMe_3$/2-propanol in CD_2Cl_2 exhibit similar signals in their ^{27}Al NMR spectra, further supporting this hypothesis.

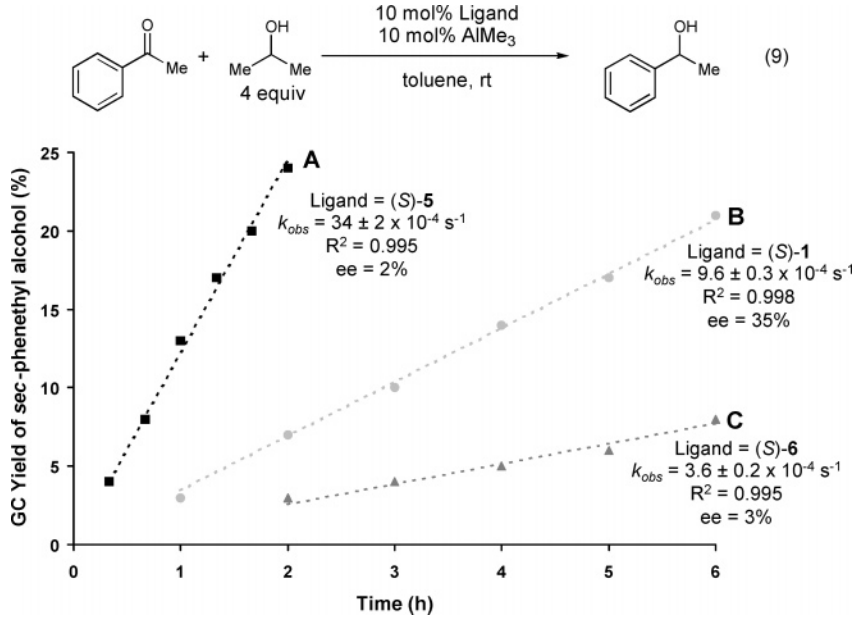
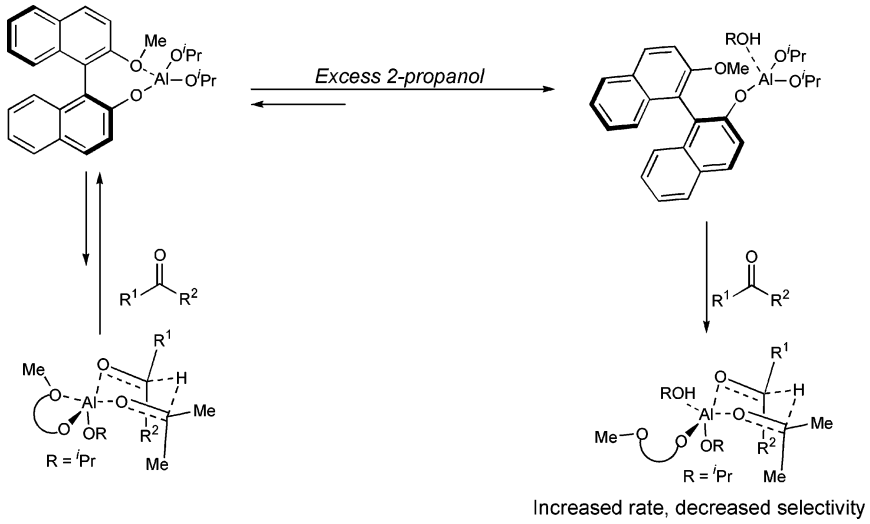


FIGURE 9. Initial rates of reaction for the MSPV reduction of acetophenone with 2-propanol, using (*S*)-**5**/$AlMe_3$ (A), (*S*)-BINOL/$AlMe_3$ (B), and (*S*)-**6**/$AlMe_3$ (C) as the catalytic precursors.

SCHEME 6. Proposed Scheme Showing the Dissociation of the Al−Ether Dative Bond in the Complex Formed between (*S*)-5 and $AlMe_3$ in the Presence of Excess 2-Propanol



the resulting anion with methyl iodide. Deprotection of the 3-methylated MOM-protected alcohol groups afforded (*S*)-**7**. The C_2-symmetric 3,3′-dimethylated BINOL variant (*S*)-**8** was synthesized via a similar procedure, except that excess ^{n}BuLi was used to afford deprotonation in both the 3 and 3′ positions of the MOM-protected (*S*)-BINOL, followed by anion trapping with excess methyl iodide and subsequent deprotection of the MOM groups. The monoethyl- ((*S*)-**9**) and diethyl-BINOL ((*S*)-**10**) derivatives were synthesized in an analogous manner, using ethyl iodide as the anion trap.

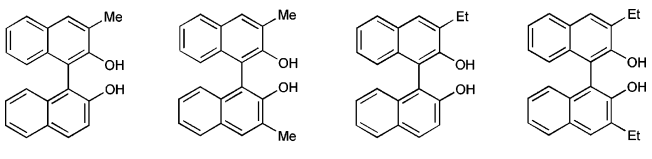


FIGURE 10. Alkyl-substituted BINOL derivatives.

The MSPV reduction of α-bromoacetophenone with 2-propanol was carried out with the in situ-formed complexes between $AlMe_3$ and ligands (*S*)-**7** through (*S*)-**10** (Table 3). While all the ligands afforded good yields of the reduced product, the selectivities of reduction were servely diminished with respect to the parent BINOL/$AlMe_3$ catalyst. While the C_2-symmetric disubstituted ligands (*S*)-**8** and (*S*)-**10** afforded 50% and 26% ee of the product, respectively (Table 3, entries 3 and 5), their monosubstituted counterparts (*S*)-**7** and (*S*)-**9** afforded no enantioselectivity (Table 3, entries 2 and 4), suggesting that C_1-symmetric ligands are inappropriate choices for the asymmetric MSPV reduction.

Interestingly, aluminum complexes incorporating (*S*)-**7** through (*S*)-**10** catalyzed the MSPV reduction of acetophenone with rates that are more than 1 order of magnitude faster than that for BINOL itself, albeit with a lower ee (Table 4 and Figure 11). Given this dramatic rate increase, we initially hypothesized that the increased steric bulk surrounding the phenol moieties of

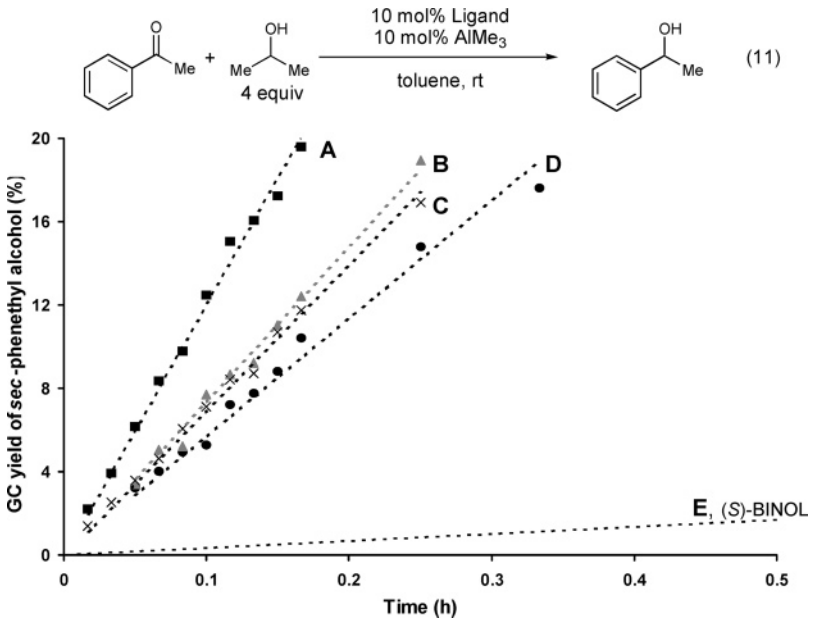
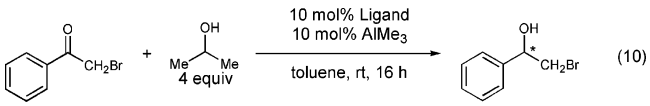


FIGURE 11. Initial reaction rates of the MSPV reduction of acetophenone with 2-propanol, using (*S*)-**7**/$AlMe_3$ (D), (*S*)-**8**/$AlMe_3$ (A), (*S*)-**9**/$AlMe_3$ (B), (*S*)-**10**/$AlMe_3$ (C), and (*S*)-BINOL (E) as the catalytic precursors. Line E was generated from the rate data obtained for (*S*)-BINOL in Figure 3.

TABLE 3. The MSPV Reduction of α-Bromoacetophenone Catalyzed by the in Situ- formed Complex between $AlMe_3$ and Substituted BINOL Derivatives (*S*)-7 through (*S*)-10



entry	ligand	GC yield [%]	ee [%]
1	(*S*)-BINOL	99	83 (*S*)
2	(*S*)-**7**	98	0
3	(*S*)-**8**	98	50 (*S*)
4	(*S*)-**9**	97	0
5	(*S*)-**10**	97	26 (*S*)

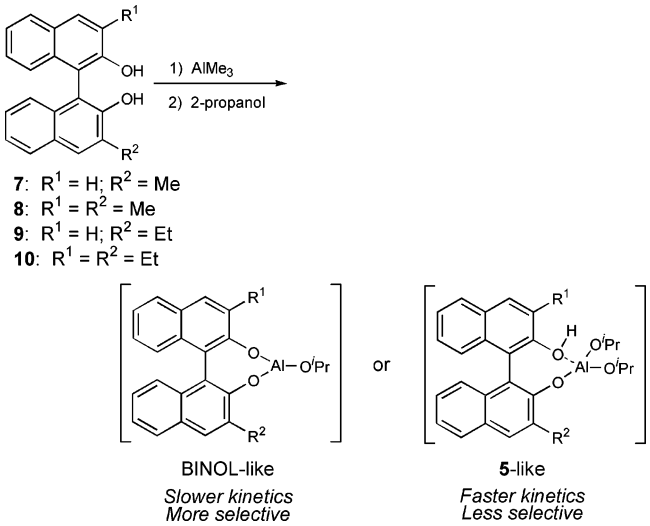
TABLE 4. Rate and Selectivity Data for the MSPV Reduction of Acetophenone with Substituted BINOL-derived Ligands

entry	ligand	line	fit parameter, R^2	$10^4 k_{obs}$ (s^{-1})	ee (%)
1	(*S*)-BINOL	E		9.6 ± 0.1	35
2	(*S*)-**7**	D	0.981	158 ± 3	13
3	(*S*)-**8**	A	0.993	333 ± 2	15
4	(*S*)-**9**	B	0.990	20 ± 2	6
5	(*S*)-**10**	C	0.996	192 ± 1	15

(*S*)-**7** through (*S*)-**10** (relative to BINOL) could potentially inhibit the full deprotonation of the ligand by $AlMe_3$, thereby preventing the formation of a species similar in structure to **1a**. Such a situation could result in the formation of tetracoordinate, monodeprotonated intermediates (Scheme 7) analogous to that formed between **5** and $AlMe_3$ (vide supra), and hence may not result in the most selective catalysts.

To evaluate the possibility that incomplete deprotonation may have occurred for (*S*)-**7** through (*S*)-**10**, we turned to NMR spectroscopy. The ^{1}H NMR spectra of a 1:1 mixture of (*S*)-**8** and $AlMe_3$ in THF-d_8 exhibited an AlMe peak at 0.95 ppm (10:3 integration ratio for the aromatics:AlMe protons) and does not contain a resonance that can be assigned to OH protons, suggesting a complete deprotonation of the ligand (Figure 12). Unlike the equivalent experiment conducted with **1**, which

SCHEME 7. Possible Modes of Reactivity between $AlMe_3$ and the Substituted BINOL Derivative (*S*)-7 through (*S*)-10



indicates a pentacoordinate geometry under MSPV reaction conditions, the ^{27}Al NMR spectrum of a 1:1:40 mixture of (*S*)-**8**/$AlMe_3$/2-propanol exhibited a signal at 70 ppm, indicative of a tetracoordinate aluminum species.[28,30] Similar results were found for ^{27}Al NMR experiments conducted with (*S*)-**7** (62 ppm), (*S*)-**9** (65 ppm), and (*S*)-**10** (74 ppm).

The dramatic increase in rate for catalysts derived from (*S*)-**8**/$AlMe_3$ and (*S*)-**10**/$AlMe_3$, relative to the (*S*)-BINOL/$AlMe_3$ combination, can be explained by their adoption of a tight tetrahedral geometry in the hydrogen transfer step. With the BINOL-derived catalyst, the less sterically encumbered aluminum site allows for deviation from this "preferred" geometry to a more sterically bulky pentacoordinate species, a geometry that previously has been suggested to be less active in the MSPV reduction.[15,16] Presumably, the tighter tetrahedral arrangement would place the transferring hydrogen in closer proximity to

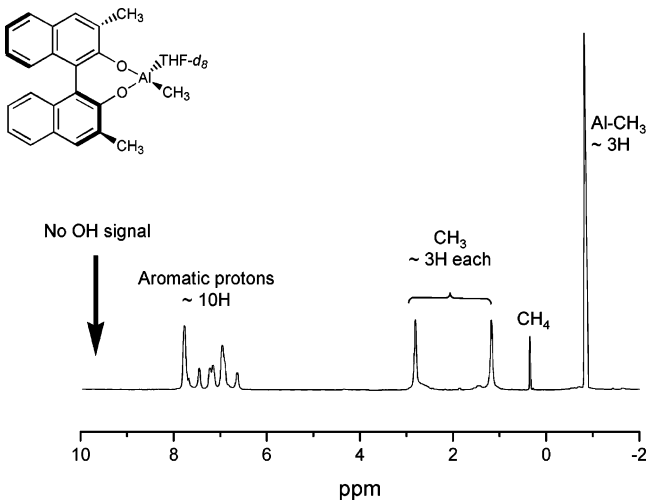
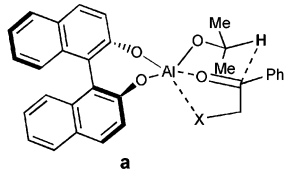
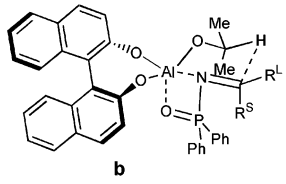


FIGURE 12. The ^{1}H NMR spectrum of the reaction between (*S*)-**8** and $AlMe_3$ indicating complete deprotonation of the ligand.



a

(*S*)-BINOL gives (*S*)-enriched reduced products



b

(*S*)-BINOL gives (*R*)-enriched reduced products

FIGURE 13. (a) Proposed 2-point coordination of α-halogenated carbonyl substrates in the asymmetric MSPV reduction catalyzed by (BINOLate)Al(O^{i}Pr), which is similar to (b) the proposed 2-point coordination of *N*-phosphinoyl ketimines to (BINOLate)Al(O^{i}Pr) in its stoichiometric reduction by the latter reagent.[47] The models shown above correctly predict the experimentally observed sense of enantioenrichment for the reduction of both α-halogenated acetophenone and *N*-phosphinoyl ketimines[47] at the (BINOLate)Al(O^{i}Pr) center.

the carbonyl carbon than in the corresponding pentacoordinate arrangement, and hence accelerates the reaction rate accordingly.

The aforementioned difference in coordination sphere also helps to explain the decreased enantioselectivity obtained in the MSPV reduction of α-bromoacetophenone for the (*S*)-**8**/$AlMe_3$- and (*S*)-**10**/$AlMe_3$-catalyzed system relative to the (*S*)-BINOL/$AlMe_3$-catalyzed system.[19] Given the ability of the (BINOLate)-Al(O^{i}Pr) species to coordinate two additional solvent molecules (vide supra), an operative explanation for the high selectivity observed for (*S*)-BINOL/$AlMe_3$ with α-halogen-containing substrates has been the ability for formation of a weak but important, 2-point coordination between the ketone substrate and the aluminum center, similar to that proposed for transition-metal-catalyzed directed hydrogenations,[45,46] thereby facilitating a more selective reduction (Figure 13a). With the (*S*)-**8**/$AlMe_3$/2-propanol and (*S*)-**10**/$AlMe_3$/2-propanol systems, where tetracoordinate intermediates have been suggested (vide supra), this 2-point coordination is not available due to steric crowding, and the enantiomeric excess of product would be depleted, as is the case. Indeed, such a 2-point binding model between a substrate and (BINOLate)Al(O^{i}Pr) has been invoked recently to explain the high enantioselectivity observed in the MSPV reduction of *N*-phosphinoyl ketimines.[47]

That the enantioselectivities obtained in the aforementioned *stoichiometric* imine MSPV reduction were considerably higher (93−98%) than that for the analogous, but *catalytic*, reduction of the α-halogenated carbonyl substrates can be rationalized via the relative binding strengths of the two substrate classes to the Al-center in (BINOLate)Al(O^{i}Pr). The *N*-phosphinoyl imines bind to the metal in a nonreversible, Lewis acid-Lewis base fashion, as is evidenced by the need for a stoichiometric amount of the aluminum reagent before the reduced amide product can be obtained in good yields. This nonlabile two-point binding, comprising both a strong Al←N and a strong Al←O═P bond (Figure 13b), results in a highly ordered transition state and thus a high level of enantioselectivity. Conversely, the α-halogenated carbonyl substrates can be reduced in high yield by using only 10 mol% of the BINOL/$AlMe_3$ mixture, indicating a more labile binding of this substrate class to the Al-center via a weak Al←O═C bond and a weak Al←X bond. While this reversible binding allows for catalyst turnover, it also holds the substrate less strongly to the Al-center, leading to an overall lower selectivity in the reduction. Further experiments to quantify this situation, as well as the evaluation of other ketone substrates capable of 2-point coordination, are currently underway.

Conclusion

In conclusion, we have obtained evidence to support the conjecture that the in situ reaction between 2,2′-dihydroxy-1,1′-binapthyl, $AlMe_3$, and 2-propanol gives rise to a monomeric, chiral aluminum alkoxide that acts as the catalyst for the MSPV reduction of ketones with 2-propanol. Through various kinetic studies, we came to the conclusion that this catalyzed MSPV reduction is likely to proceed through a monometallic activation of the substrates with a direct, concerted hydrogen transfer from the bound alkoxide to the carbonyl carbon. Importantly, reversibility does not seem to plague the asymmetric efficacy of the BINOL/$AlMe_3$ catalyst system under the employed MSPV experimental conditions, with the enantiomeric excess of the reduced product remaining constant for many hours after the reduction. The use of a high excess of 2-propanol inhibits the aluminum-catalyzed MSPV reduction, presumably locking the aluminum center in an inactive, substrate-less, pentacoordinate state.

From a ligand design perspective, the use of bidentate, chiral phenol-based ligands in aluminum-catalyzed MSPV reduction not only imparts the necessary asymmetric environment around the aluminum center, but also dramatically increases the reaction rate. While BINOL ether ligands can also lead to an active catalytic aluminum species, the inherent lower coordinating ability of the ether group, in comparison to the anionic alkoxy moiety in the parent system, is a liability in the asymmetric realm, leading to decreased product selectivities. In a similar vein, crowding the ligand environment around the Al center with substitutions of the BINOL framework can enforce a tetrahedral intermediate that may lead to a faster reduction rate at the expense of selectivity. Most importantly, the ability of the (BINOLate)Al(O^{i}Pr) center to accommodate 2-point coordination with a substrate, as in the case of α-halogenated ketones or *N*-phosphinoyl ketimines, is critical to the generation of high

enantiomeric excess in product. This multidentate substrate coordination mode, akin to those seen in substrate-specific biological catalysts, subtly balances catalytic activity and enantioselectivity in the BINOL/$AlMe_3$ system and suggests an additional strategy that can be exploited for developing highly selective functional group transformations.

Experimental Section

General Procedure for the Reduction of Ketone Substrates by 2-Propanol Catalyzed with the in situ-Formed Complexes between Ligands and $AlMe_3$. In an inert-atmosphere glovebox, an 8-mL vial equipped with a magnetic stirring bar was charged with ligand (0.1−0.2 mmol) and internal standard-containing anhydrous toluene (4 mL). $AlMe_3$ (9.6 μL, 0.1 mmol) was added via syringe and the reaction was stirred. After 0.5 h, 2-propanol (305 μL, 4.0 mmol) was added, the vial was capped with a Teflon-lined silicone septa, and the reaction was stirred for an additional 0.5 h. Either acetophenone (115 μL, 1.0 mmol) or α-bromoacetophenone (198 mg, 1.0 mmol) was added neat; the reaction was taken out of the glovebox and stirred at room temperature. At the indicated time, a 100-μL aliquot of the reaction was collected with a gas-tight syringe, loaded onto a plug of alumina, rinsed with methanol (15 mL), and analyzed directly by GC and chiral GC. GC method for acetophenone reductions: start temperature = 80 °C, initial time = 4 min, ramp = 5 deg/min, final temperature = 100 °C, final time = 2 min; retention times: *sec*-phenethyl alcohol = 4.24 min, acetophenone = 4.40 min. GC method for α-bromoacetophenone reductions: start temperature = 110 °C, initial time = 4 min, ramp = 5 deg/min, final temperature = 150 °C, final time = 2 min; retention times: α-bromomethylbenzyl alcohol = 6.07 min, α-bromoacetophenone = 6.29 min. Chiral GC method for acetophenone reductions: start temperature = 80 °C, initial time = 20 min, ramp = 5 deg/min, final temperature = 170 °C, final time = 10 min; retention times of *sec*-phenethyl alcohol enantiomers: 29.72 min (*S*) and 30.32 min (*R*). Chiral GC method for α-bromoacetophenone reductions: start temperature = 100 °C, initial time = 0 min, ramp = 2 deg/min, final temperature = 170 °C, final time = 10 min; retention times of α-bromomethylbenzyl alcohol enantiomers: 34.95 min (*S*) and 35.57 min (*R*).

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Supporting Information Available: General synthetic procedures, detailed experimental conditions, kinetic data, and characterization data, as well as *XYZ* coordinates of the crystal structure (*S*)-**2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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