JOC*Note*

Highly Diastereoselective Catalytic Meerwein−Ponndorf−Verley Reductions

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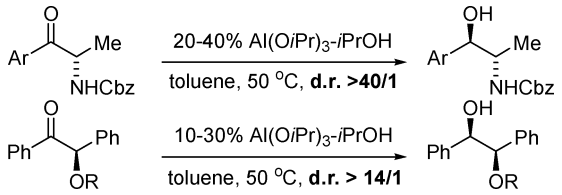

Very practical synthesis of ephedrine analogues in high yields and enantiopurity was realized by a highly diastereoselective Meerwein−Ponndorf−Verley (MPV) reduction of protected α-amino aromatic ketones using catalytic aluminum isopropoxide. The high anti selectivity resulted from the chelation of the nitrogen anion to the aluminum. In contrast, high syn selectivity was obtained with α-alkoxy ketones and other compounds via Felkin−Ahn control.

The Meerwein−Ponndorf−Verley (MPV) reduction of ketones and aldehydes has been known for 80 years.[1] It generally uses inexpensive and environmentally friendly ^{i}PrOH as a hydride source and aluminum alkoxides as catalysts, and the reaction is chemoselective, easy to operate, and readily scalable.[2] These apparent practical advantages make the MPV reduction a particularly attractive green-chemistry approach for reduction of carbonyl compounds. However, aluminum-mediated MPV reduction is limited by its requirement of a stoichiometric amount of the aluminum alkoxide catalyst and sometimes low yields due to side reactions.[2] A number of modified aluminum catalyst systems have been designed for catalytic MPV reductions,[3] but they either give side reactions due to increased Lewis acidity[3a] or require complex ligands[3b−d] or pyrophoric starting materials.[3e] Additionally, although enantioselective aluminum-catalyzed MPV reduction has met with moderate success,[2c] MPV reduction in general has not attracted much attention as a stereoselective reduction method.[4] In the few examples of MPV reductions with reported high diastereoselectivities, stoichiometric amounts of aluminum alkoxides were used.[5] Therefore, MPV reduction has seen very limited applications for diastereoselective reductions in modern synthetic organic chemistry, and various boron hydrides and aluminum hydrides are usually the preferred agents. To realize the full potential of the MPV reduction, it is important to develop *catalytic and highly stereoselective* processes. Here, we report such a process for the syntheses of ephedrine analogues and monoprotected 1,2-diols.

Ephedrine and its analogues (**4**) are widely used as chiral auxiliaries[6] and chiral resolution agents[7] and also have important implications in weight control and treatment of obesity.[8] As shown in Scheme 1,[9] **4** could be obtained by direct $LiAlH_4$ reduction of **3**, whose precursor **2** could be readily prepared from commercially available enantiopure carbamate-protected alanine **1** (X = OH) via activation as an acyl chloride or a Weinreb amide [X = Cl or NMe(OMe)].[10] $PhMe_2SiH$−TFA was the most effective condition for the key diastereoselective reduction of **2** [diastereomeric ratio (d.r.) > 98:2],[9b,c] but the relatively high cost of $PhMe_2SiH$ and use of TFA as solvent limited the application of this method on a large scale.

We were interested in developing a practical reduction of the aminoketone **2**−**3** and started by screening the commonly used reducing agents for this reaction (Table 1). The bistrifluoromethyl ketone **2a** was a good substrate because of its high reactivity and good compatibility of CF_3 groups to various reducing agents.[11]

The TFA−$PhMe_2SiH$ procedure[9b,c] did give a very high d.r. (entry 1), but the use of a cheaper silane Et_3SiH resulted in slow and incomplete reactions. Among various borohydrides (entries 2−10), only $NaB(OAc)_3H$ gave a reasonable d.r. of 4.9:1 (entry 9); however, this reaction was sluggish, and attempts to further optimize it failed. Simple aluminum hydrides such as $LiAlH_4$ and $LiAl(O^{t}Bu)_3H$ gave moderate undesired selectivities

(1) (a) Meerwein, H.; Schmidt, R. *Justus Liebigs Ann. Chem.* **1925**, *444*, 221. (b) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138. (c) Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871.

(2) Reviews: (a) Wilds, A. L. *Org. React.* **1944**, *2*, 178. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007. (c) Nishide, K.; Node, M. *Chirality* **2002**, *14*, 759.

(3) (a) Kow, R.; Nygren, R.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 826. (b) Ko, B.-T.; Wu, C.-C.; Lin, C.-C. *Organometallics* **2000**, *19*, 1864. (c) Konishi, K.; Makita, K.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1988**, 643. (d) Ooi, T.; Miura, T.; Maruoka, K. *Angew Chem., Int. Ed.* **1998**, *37*, 2347. (e) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391.

(4) The MPV reduction was generally not considered to give good diastereoselectivities. See ref 2a.

(5) (a) Lund, H. *Ber.* **1937**, *70B*, 1520. (b) Jackman, L. M.; Macbeth, A. K.; Mills, J. A. *J. Chem. Soc.* **1949**, 2641. (c) Banthorpe, D. V.; Davies, H. ff. S. *J. Chem. Soc. B* **1968**, 1356. (d) Mueller, H. K.; Schuart, J.; Baborowski, H. *J. Prakt. Chem.* **1973**, *315*, 1045. (e) Hach, V. *J. Org. Chem.* **1973**, *38*, 293. (f) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1185. (g) Hilpert, H. EP 703209, 1996. (h) Satoh, H.; Yamamoto, K. EP 934923, 1999. (i) Matsuo, K.; Matsumoto, S.; Inoue, K. WO 9855452, 1998. (j) Brown, J. D.; Cain, R. O.; Kopach, M. E. EP 963972, 1999. (k) Urban, F. J.; Jasys, V. J. *Org. Process Res. Dev.* **2004**, *8*, 169.

(6) Selected examples: (a) Rueck, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433. (b) Anakabe, E.; Badia, D.; Carrillo, L.; Rodriguez, M.; Vicario, J. L. *Trends Org. Chem.* **2001**, *9*, 29.

(7) *Enantiomers, Racemates, and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; Krieger: Malabar, FL,1991.

(8) Selected examples: (a) Clapham, J. C. *Curr. Drug Targets* **2004**, *5*, 309. (b) Dulloo, A. G. *Int. J. Obes.* **2002**, *26*, 590.

(9) (a) Buckley, T. F., III.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157. (b) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (c) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415.

(10) (a) Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letts, G.; Rosentha, A. S. *J. Med. Chem.* **1992**, *35*, 641. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331.

(11) Unlike many other ketones in Table 2, the product isomers **3a**/**5a** are readily separated by LC for easy analysis during screening.

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SCHEME 1

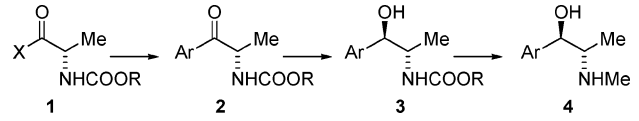
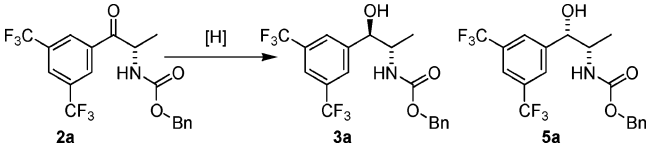


TABLE 1. Reducing Agents Screening



entry	reducing agents	solvent	temp (°C)	time (h)	conv (%)	**3a**/**5a**
1	TFA−$PhMe_2SiH$	TFA	−5	15	99	64
2	$NaBH_4$	MeOH	−78	1	100	0.71
3	Bu_4NBH_4	THF	0	2	100	1.3
4	$Zn(BH_4)_2$	THF	−78[a]	3	100	2.3
5	$Zn(BH_4)_2$	MeOH	−78	1	100	0.63
6	$LiBH_4$	THF	−5	2	100	1.3
7	9-BBN	THF	rt	16	33	2
8	$LiB(^sBu)_3H$	THF	−78	2	97	0.71
9	$NaB(OAc)_3H$	THF	20	72	93	4.9
10	$NaB(OAc)_3H$−HOAc	DMAc	20	72	60	1.9
11	$LiAl(O^tBu)_3H$	THF	−40	1	95	0.55
12	$LiAlH_4$	THF	−78	0.5	100	0.45
13	DIBAL	toluene	−78	2	100	12
14	DIBAL	tol−THF	−78	0.5	100	8.4
15	$Al(^iBu)_3$	toluene	−78	0.7	74	11
16	Et_2AlCl	toluene	0	0.5	45[b]	8.5
17	Et_2Zn	toluene	rt	16	30[b]	
18	DIBAL−$ZnCl_2$	toluene	−78	0.2	95	10
19	DIBAL−BHT	toluene	−78[a]	16	100	13
20	DIBAL−IPA (1:1)	toluene	20	120	80	20
21	DIBA−-EtOH (1:1)	toluene	20	96	85[c]	17
22	DIBAL−MeOH (1:1)	toluene	20	96	90[c]	9.8
23	DIBAL−^{t}BuOH (1:1)	toluene	20	120	10	3.7
24	DIBAL−menthol (1:2)	toluene	20	120	75	29
25	20% DIBAL−12 equiv IPA	toluene	20	3	48	120
				18	62	118
26	0.2 equiv $Al(O^iPr)_3$−11 equiv IPA	toluene	20	18	22	91
27	0.2 equiv $Al(O^iPr)_3$−11 equiv IPA	toluene	50	18	100	76

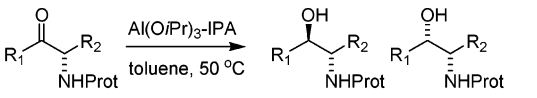
[a] Warmed to room temperature (rt) at the end. [b] Some Et adduct. [c] Not clean.

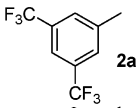
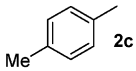
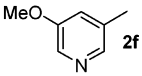
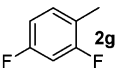
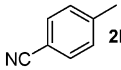
(entries 11 and 12). However, DIBAL (diisobutylaluminum hydride) in toluene gave a good selectivity of 12:1 (entry 13). The d.r. dropped when THF was used as a cosolvent (entry 14). Interestingly, $Al(^iBu)_3$ alone gave a high d.r. of 11:1 (entry 15), indicating a hydride transfer from the alkyl group. Other alkylmetal reagents for reduction were less efficient (entries 16 and 17).

Modification of DIBAL by adding $ZnCl_2$ resulted in a slightly lower d.r. (entry 18). Addition of BHT to DIBAL,[12] however, gave a slightly higher d.r. (entry 19), and this prompted us to screen other cheaper proton sources to modify DIBAL. Although the reaction became very slow, addition of 1 equiv of ^{i}PrOH (IPA) gave an excellent d.r. of 20:1 (entry 20). Other alcohols were less efficient (entries 21−23). Addition of 2 equiv of menthol to DIBAL would leave no isobutyl group for hydride

(12) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

TABLE 2. Diastereoselective MPV Reduction of Protected Aminoketones[a]



Entry	R_1	R_2	Prot	eq Al	time (h)	**3**/**5**[b]	yield (%)[c]
1	 **2a**	Me	Cbz	0.20	15	98.7/1.3	97[d]
2	 **2b**			0.30	15	>99/1	95
3	 **2c**			0.30	48	>99/1	90
4	 **2d**			0.40	24	>99/1	86
5	 **2e**			0.20	18	>99/1	96[d]
6	 **2f**			0.60	48	>99/1	82
7	 **2g**			0.30	40	97.6/2.4	93
8	 **2h**			0.40	60	98.4/1.6	91
9	$ClCH_2$- **(2i)**	Bn	Cbz	0.30	18	96.1/3.9	94
10	$ClCH_2$- **(2j)**	Bn	Tos	0.30	18	82/18	100[e]

[a] Reaction conditions: A mixture of ketone (0.637 mmol, 1.0 equiv), $Al(O^iPr)_3$ (0.2−0.6 equiv), and ^{i}PrOH (0.536 mL, 11 equiv) in toluene (0.80 mL) was heated at 50 °C. [b] Based on crude ^{1}H NMR or LC. [c] Isolated yields. [d] 99% ee from 99% ee SM. [e] Combined yield of both isomers.

transfer,[13] but the reaction still proceeded with a very high d.r. of 29 (entry 24), indicating a highly diastereoselective α-hydride transfer from an aluminum alkoxide, i.e., MPV reduction.

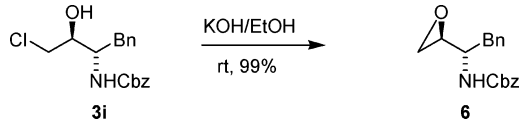
Indeed, with a combination of 20% DIBAL and 12 equiv of IPA,[14] the MPV reduction proceeded in an excellent d.r. (120:1) to 48% conversion at room temperature in 3 h but slowed significantly afterward (entry 26).[15] Use of commercial $Al(O^iPr)_3$ resulted in a slower reaction (entry 26), but complete conversion was achieved by simply raising the temperature to 50 °C (entry 27). It is also critical to discover that *no racemization* was observed. Thus, highly diastereoselective MPV reduction of carbamate-protected aminoketone **2** was developed using a catalytic amount of the simple and practical

(13) N−H of the carbamate on **2a** provides the third equiv of a proton to fully quench DIBAL's two isobutyl groups and one hydride.

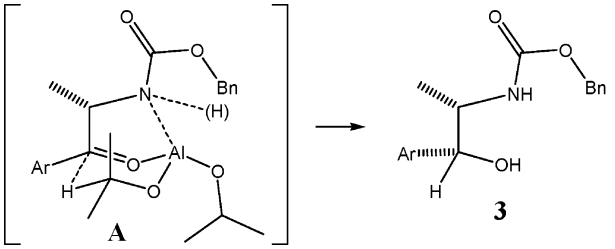
(14) An excess of IPA was required, as the reaction using 2 equiv of $Al(O^iPr)_3$ without IPA was very sluggish. It has been proposed that IPA can help convert the tetramer of aluminum isopropoxide to the much more reactive form (~2.8 oligomer). Shiner, V. J.; Whittaker, D. *J. Am. Chem. Soc.* **1969**, *91*, 394.

(15) The fast initial reaction rate suggests the higher activity of the freshly prepared $Al(O^iPr)_3$, as observed in ref 3e. The slow rate afterwards was comparable to the rate using commercial $Al(O^iPr)_3$, suggesting the deactivation of the catalyst to a less active form during the reaction.

SCHEME 2



SCHEME 3



$Al(O^iPr)_3$, which offers significant advantages over the TFA−silane procedure in terms of costs, potential functional group compatibility, environmental aspects, scalability, and ease of operation/isolation/waste control.

The MPV reduction proved to be applicable to various N-protected α-aminoketones (Table 2). With Cbz as the protecting group, very high diastereoselectivities (97.6:2.4 to >99:1) and excellent yields of the anti products **3** were obtained for all ephedrine-type substrates. No racemization was observed for an electron-deficient substrate (entry 1) or an electron-rich one (entry 5). $NaBH_4$ reduction in MeOH at room temperature was carried out for each ketone to obtain the syn isomer **5** for selectivity measurements of the MPV reductions by ^1H NMR or liquid chromatography (LC) (entries 1 and 4), and the **3**/**5** ratio with $NaBH_4$ ranged from 2.1:1 to 3.8:1. Aryl groups with electron-withdrawing substituents (entries 1,7, and 8) or electron-donating substituents (entries 3−5) and with steric hindrance (entries 4 and 5) were tolerated. In most cases, 20−30% of the aluminum catalyst was enough, but the ketone with a pyridyl group required up to 60% of $Al(O^iPr)_3$ for >95% conversion (entry 6), likely due to partial deactivation of the catalyst by the pyridine ring.[16] The α-chloromethyl group in place of an aryl group was also tolerated to give product **3i** (entry 9), which could be readily converted to α-aminoepoxide **6**, an advanced building block for aminodiol HIV protease inhibitors (Scheme 2).[17]

When a mixture of **3d**/**5d** in a ratio of 2.9:1 was spiked into the MPV reduction of **2b** using 0.40 equiv of $Al(O^iPr)_3$, **3d**/**5d** was recovered in about the same ratio after 24 h at 50 °C, suggesting that the high anti selectivity is kinetically controlled.[18]

The observed anti selectivity agrees with the chelation control (Scheme 3). This is also supported by the fact that NTos in **2j**, a more electron-deficient and weaker chelating group, gave a lower selectivity of 82:18 (entry 10).

To determine if other substituents such as an alkoxy group have the same chelation control, benzoin monomethyl ether was subjected to the MPV reduction (Scheme 4). Surprisingly,

SCHEME 4

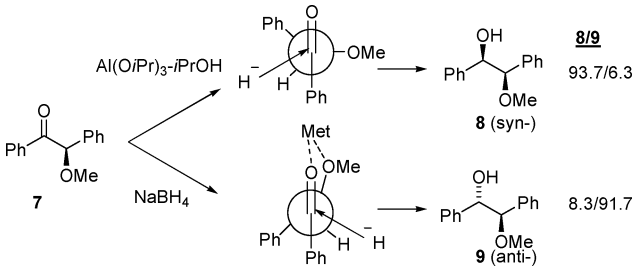
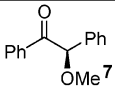
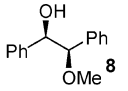
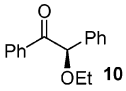
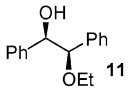
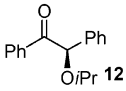
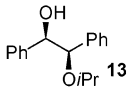
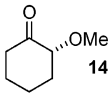
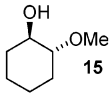
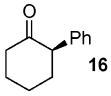
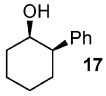


TABLE 3. Diastereoselective MPV Reduction without Chelation Control[a]

Entry	ketone	main prdt	eq Al	time (h)	d.r.[b]	yield (%)[c]
1	 **7**	 **8**	0.10	40	93.7/6.3	100
2	 **10**	 **11**	0.20	22	95.5/4.5	95
3	 **12**	 **13**	0.30	18	96.1/3.9	98
4	 **14**	 **15**	0.20	16	86/14	(97)
5	 **16**	 **17**	0.20	19	83/17	100

[a] Reaction conditions: a mixture of racemic ketone (2.55 mmol, 1.0 equiv), $Al(O^iPr)_3$ (0.1−0.3 equiv), and ^iPrOH (2.15 mL, 11 equiv) in toluene (3.2 mL) was heated at 50 °C. [b] Based on crude ^1H NMR or LC. [c] Isolated combined yield of both isomers; NMR yield in parentheses.

instead of the chelation-controlled anti product **9**, the Felkin−Ahn-controlled syn product **8** was the main product. This is the only reported highly syn-selective reduction of **7**.[19] $NaBH_4$ gave a high ratio of the anti product **9**.[20]

The MPV reductions of other α-alkoxy ketones also gave very high levels of Felkin−Ahn control (Table 3, entries 2 and 3). Only 10−30% of the catalyst was required. The d.r. increased with the size of the alkoxy group. The opposite selectivities observed for 2-methoxy cyclohexanone (**14**) and 2-phenyl cyclohexanone (**16**) indicated an equatorial transfer of the hydride and the preference for an axial 2-methoxy group vs an equatorial 2-phenyl group in the cyclohexanone.

The drastic difference in the chelation abilities of a NHCbz group and a MeO group in the MPV reduction was puzzling at first but can be explained by the deprotonation of the NH to generate a nitrogen anion for better chelation; the same model

(16) It was found that addition of a catalytic amount of bipyridine resulted in a slower MPV reduction.

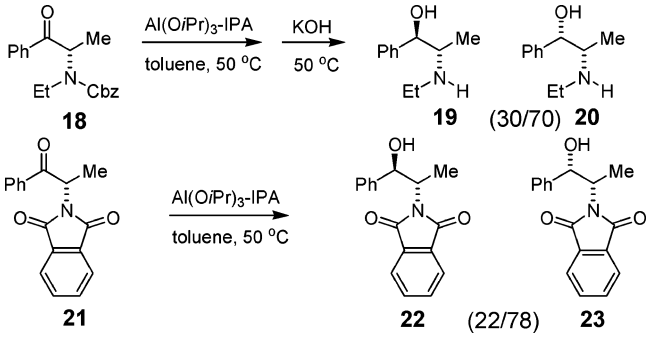
(17) (a) Bisacchi, G. S.; Ahmad, S.; Alam, M.; Ashfaq, A.; Barrish, J.; Cheng, P. T. W.; Greytok, J.; Hermsmier, M.; Lin, P. F.; Merchant, Z.; Skoog, M.; Spergal, S.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 459. For a review, see: (b) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243.

(18) We also observed about the same d.r. at 3 h (~60% conv) as that at 18 h for the MPV reduction of **2a**.

(19) A moderate d.r. (**8**/**9** ~2:1) has been reported using other methods: (a) Burk, M. J.; Harper, T. G. P.; Lee, J. R.; Karberg, C. *Tetrahedron Lett.* **1994**, *35*, 4963. (b) Shibata, I.; Yoshida, T.; Kawakami, T.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 4049.

(20) Most other reducing agents also gave high anti/syn ratios: (a) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021. (b) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929. (c) Abernethy, C. D.; Cole, M. L.; Davies, A. J.; Jones, C. *Tetrahedron Lett.* **2000**, *41*, 7567.

SCHEME 5



was proposed in the highly anti-selective reduction of chloromethyl ketones using $LiAl(O^tBu)_3H$ in EtOH at −78 °C.[21] To gain more insight, the hydrogen in **2b** was replaced with an ethyl group (**18**) and subjected to the MPV reduction (Scheme 5). Interestingly, after hydrolysis to remove the protecting group, the anti/syn ratio was a reversed 30:70, disfavoring the chelation-controlled anti product **19**.[22,23] MPV reduction of **21** also disfavored the chelation-controlled product **22** with an anti/syn ratio of 22:78. All these support the model of chelation with a nitrogen anion, which forms by proton exchange between the NHCbz group and the aluminum alkoxide.

In summary, the catalytic MPV reduction of Cbz-protected α-amino aromatic ketones shows very high anti/syn selectivity and provides an exceedingly practical preparation of ephedrine-type products in high diastereo- and enantiopurity. The reaction likely proceeds through chelation with deprotonated carbamate. Without the chelation control, the $Al(O^iPr)_3-{}^i$PrOH system functions as a bulky hydride source to give very high syn/anti selectivities, especially for α-alkoxy ketones. Therefore, it is important to note that, for diastereoselective reductions of carbonyls, the highly practical catalytic MPV reduction is an excellent option in both chelation-controlled and Felkin−Ahn-controlled settings.

(21) Hoffman, R. C.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045.

(22) In this case, $NaBH_4$ gave an anti/syn selectivity of 94:6.

(23) Direct MPV reduction on 2-(ethylamino)propiophenone hydrochloride to give **19**/**20** was unsuccessful possibly because of the reaction between the amino group and the ketone.

Experimental Section

Representative Procedure for MPV Reduction. A mixture of ketone **2a** (267 mg, 0.637 mmol, 1.0 equiv), $Al(O^iPr)_3$ (26 mg, 0.2 equiv), and ^{i}PrOH (0.536 mL, 11 equiv) in toluene (0.80 mL, 1.3 mL/mmol) was heated at 50 °C under N_2 for 15 h. The reaction was cooled and quenched with 4 mL of 1 N HCl and 4 mL of EtOAc. The organic layer was washed with 4 mL of water and concentrated. Crude ^{1}H NMR was taken to determine the diastereoselectivity to be 98.3:1.7. The product was further purified by a hexane tituration to give 260 mg (97% yield) of (1*R*,2*S*)-1-(3′,5′-bistrifluoromethylphenyl)-2-benzyloxycarbonylamino-1-propanol (**3a**) as a white solid with >99% enantiomeric excess (ChiralPak AD-H (4.6 × 150 mm) column, 0.1:10:90 of TFA/^{i}PrOH/heptane, 1.5 mL/min at 30 °C; retention times for desired 1*R*,2*S* enantiomers of 2.6 min and for undesired, 4.7 min). Mp 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 9.6 Hz, 3 H), 7.33−7.40 (m, 5 H), 5.14 (s, 2 H), 5.05 (br s, 1 H), 4.95 (br d, J = 4.4 Hz, 1 H), 4.06 (br s, 1 H), 3.40 (br s, 1 H), 1.01 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 143.5, 136.0, 131.5 (q, J = 33.3 Hz), 128.6, 128.4, 128.1, 126.5 (m), 123.3 (q, J = 273 Hz), 121.5 (m), 75.3, 67.3, 52.5, 13.9. Anal. Calcd for $C_{19}H_{17}F_6NO_3$: C, 54.16; H, 4.07; N, 3.32. Found: C, 54.15; H, 3.84; N, 3.29.

Characteristic ^{1}H NMR signals for the minor isomer: 1.21 (d, J = 6.9 Hz, 3 H).

Supporting Information Available: Experimental procedures and characterization data for reduction products (Tables 2 and 3) and compounds **18**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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