

Enantioselective MSPV Reduction of Ketimines Using 2-Propanol and (BINOL)Al^{III}

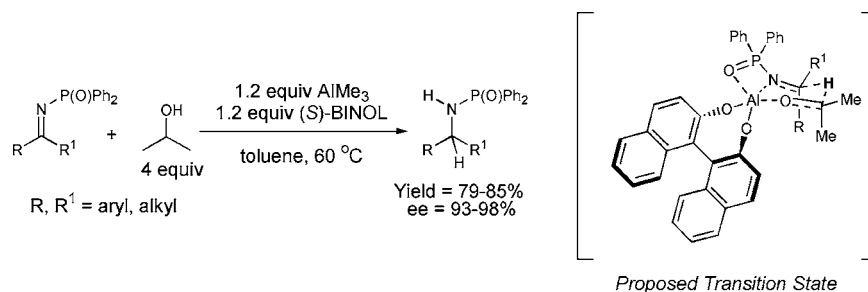
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ABSTRACT



A highly enantioselective Meerwein–Schmidt–Ponndorf–Verley (MSPV) reduction of *N*-phosphinoyl ketimines by (BINOL)Al^{III}/2-propanol is reported. Yields ranging between 79 and 85% with high enantiomeric excesses (93–98%) are observed for a wide range of structurally diverse ketimines. A [2.0.4] bicyclic chelation model is proposed to account for this high selectivity.

The synthesis of chiral secondary amines is an important endeavor given the extensive presence of this functional group in natural products, pharmaceutical agents, and fine chemicals.¹ While several synthetic pathways toward this class of compounds can be envisioned,^{1c} one of the most standard routes is the direct enantioselective reduction of prochiral ketimines.^{2,3} In contrast to the major successes in the asymmetric reduction of ketones,⁴ practical and highly stereoselective strategies for the corresponding ketimine

reductions are not as prevalent.^{3,5} Prominently, Noyori has reported a protocol for the ruthenium-catalyzed asymmetric transfer hydrogenation of imines with a formic acid–triethylamine mixture.^{5f} While high asymmetric induction was obtained for cyclic *N*-benzylic imines, there was a marked decrease in selectivity for the corresponding reduction of exocyclic and acyclic *N*-alkyl substrates. Hence, the asymmetric reduction of other classes of imines, especially

(1) For examples, see: (a) Clifton, J. E.; Collins, I.; Hallet, P.; Hartley, D.; Lunts, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670–679. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (c) Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393–408. (d) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667–3675.

(2) Brunel, J. M. *Rec. Res. Dev. Org. Chem.* **2003**, *7*, 155–190.

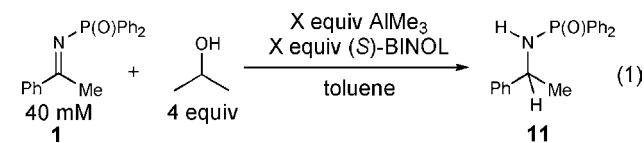
(3) Spindler, F.; Blaser, H.-U. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag GmbH & Co: Weinheim, Germany, 2004; Vol. 2, pp 113–123.

(4) For relevant reviews, see: (a) Singh, V. K. *Synthesis* **1992**, *7*, 607–617. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. (c) Fehring, V.; Selke, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1827–1830. (d) Itsuno, S. *Org. React.* **1998**, *52*, 395–576. (e) Wills, M.; Hannedouche, J. *Curr. Opin. Drug Discov. Devel.* **2002**, *5*, 881–891.

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those containing easily removable *N*-protecting groups, continues to be a major research focus in synthetic organic chemistry.⁵ At the same time, reduction strategies that circumvent the use of transition metals and metal hydrides have attracted significant attention in recent years due to the increasing demand for environmentally friendly, inexpensive, and efficient synthetic methods. The aluminum-based Meerwein–Schmidt–Ponndorf–Verley (MSPV) reduction^{6–8} is a reaction that not only satisfies these criteria but also holds substantial promise for further asymmetric developments. While employing an inexpensive and innocuous metal, this reaction proceeds under relatively mild conditions and utilizes simple secondary alcohols, such as 2-propanol, as the reducing agent.⁹ A catalytic protocol for our aluminum-based enantioselective MSPV reduction of ketones employing a chiral complex formed in situ between enantiomerically pure 2,2'-dihydroxy-1,1'-binaphthyl (BINOL),¹⁰ AlMe₃, and 2-propanol has recently been reported.^{11,12} In this paper, we disclose a highly enantioselective reduction of *N*-phosphinoyl ketimines based on the use of this reagent combination.

Table 1. Optimization of the MSPV Reduction of Ketimine **1**



entry	<i>T</i> (°C)	<i>X</i> equiv	conversion ^a (%)	ee ^b (%)
1	25	1.0	0	<i>c</i>
2	40	1.0	50	99
3	60	1.0	85	91
4	80	1.0	99	84
5	60	1.2	92	96
6	60	0.1	8	<i>c,d</i>

^a Determined by GC at 20 h. ^b Determined by chiral HPLC (Chiralcel OD-H column). ^c Not determined. ^d 80 mM in imine.

The identification of a viable imine electrophile to pair with our aluminum system was a critical first step. Encouraged by our recent success in the addition of acyl anions to *N*-diphenylphosphinoyl imines,¹³ we reasoned that these electrophilic compounds might also undergo MSPV reduction. Furthermore, these imines have recently been employed as electrophiles in a number of asymmetric transformations,^{14,15} and the resulting amides are easily converted into useful intermediates.¹⁶ Hence, we were gratified to observe the stereoselective reduction of imine **1** by 2-propanol in the presence of stoichiometric amounts of (*S*)-BINOL and AlMe₃ during our initial experiments (Table 1). While reaction 1 does not proceed at room temperature (Table 1, entry 1), quantitative conversion is observed at 80 °C, albeit in 84% ee (Table 1, entry 4). Lowering the reaction temperature to

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(7) Ponndorf, W. *Z. Angew. Chem.* **1926**, *39*, 138–143.

(8) Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871–874.

40 °C results in an increase in enantioselectivity (99% ee), but a decrease in conversion to 50% (Table 1, entry 2). Ultimately, increasing the concentration (to 80 mM) and temperature (to 60 °C) with 1.2 equiv of (*S*)-BINOL/AlMe₃ affords the desired amide **11** in 92% conversion with excellent selectivity (96% ee, Table 1, entry 5). The use of a catalytic amount of the (*S*)-BINOL/AlMe₃ mixture only affords a commensurate conversion of the imine, suggesting a single-turnover event (Table 1, entry 6).

Table 2. Reaction Scope of the MSPV Reduction of Ketimines

entry	imine	yield ^a (product)		ee ^b (%)	
		Aryl	Alkyl		
1	1	Ph	Me	85% (11)	96
2	2	Ph	Et	85% (12)	95
3	3	Ph	ⁿ Pr	84% (13)	94
4	4	Ph	ⁱ Pr	79% (14)	96
5	5	1-naphthyl	Me	80% (15)	98
6	6	2-naphthyl	Me	84% (16)	96
7	7			84% (17)	94
8	8			80% (18)	94
9	9			84% (19)	94
10	10			85% (20)	93

^a Isolated. ^b Determined by chiral HPLC (Chiralcel OD-H column).

The conditions of Table 1, entry 5, are highly selective for a wide range of structurally diverse *N*-phosphinoylimines. For example, alkyl aryl ketimines **1–6** were all reduced in good yield and excellent selectivity (Table 2, entries 1–6). The α,β -unsaturated imines **7** and **8** were also reduced with superb selectivity (Table 2, entries 7 and 8). The doubly

(9) For reviews, see: (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017. (b) Graves, C. R.; Campbell, E. J.; Nguyen, S. T. *Tetrahedron: Asymmetry* **2005**, *16*, 3460–3468.

(10) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897.

(11) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1020–1022.

(12) Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796–14803.

(13) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366.

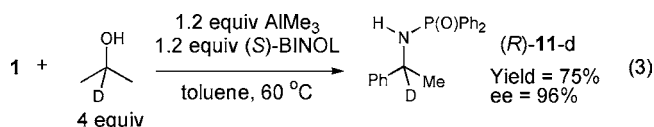
(14) For examples, see: (a) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, *26*, 493–494. (b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635 and references therein. (c) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093. (d) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, *8*, 1205–1227.

(15) For recent examples of the asymmetric reduction of phosphinoyl imines, see ref 5b,h,j,k.

(16) Kenner, G. W.; Moore, G. A.; Ramage, R. *Tetrahedron Lett.* **1976**, *17*, 3623–3626.

aliphatic ketimine **9** undergoes reduction with an unprecedented level of stereocontrol (94% ee, Table 2, entry 9).^{5b,k} Remarkably, the asymmetric environment around the Al center can even distinguish the subtle difference between *primary alkyl groups*! For example, substrate **10** with similar pentyl and ethyl substituents is converted to the amide with outstanding stereocontrol (93% ee). Although not directly comparable to the reported substrate scope of the BINAL-H system^{5b} due to differences in operating temperatures, our BINOL/AlMe₃ outperforms BINAL-H in every reported instance.

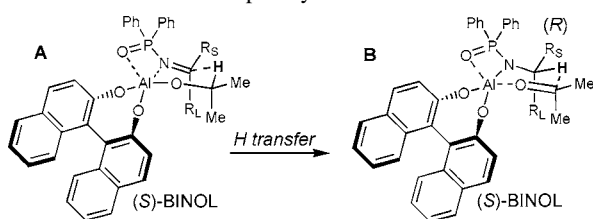
Significantly, the (BINOL)Al^{III} system can be easily employed for the enantioselective synthesis of α -deuterated secondary amides.¹⁷ Using our optimized conditions, 2-propan-2-*d*-ol successfully reduces **1** to the corresponding α -deuterated amide (*R*)-**11-d** (eq 3). With this general approach, (*R*)-(BINOL)Al^{III} and 2-propan-2-*d*-ol readily convert **1** to (*S*)-**11-d** and **10** to (*S*)-**20-d** (see Supporting Information).



Although BINOL is relatively inexpensive when purchased in bulk,¹⁸ such a valuable chiral auxiliary should be recovered. For this purpose, we have developed a simple and practical acid–base extraction sequence. Compound **1** can be reduced on a 1-g scale to **11** in 75% isolated yield (96% ee) and 93% recovery of the BINOL ligand, which was reused in a subsequent reduction of **1** to afford **11** in 95% ee (90% conversion of **1**, see Supporting Information).

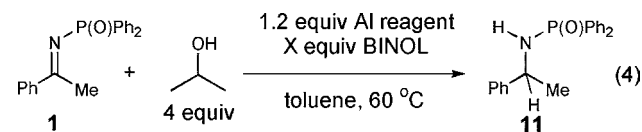
The exquisite selectivity exhibited by the BINOL/AlMe₃ combination can be attributed to a four-membered chelation of the aluminum center by the iminophosphinoyl functionality, similar to those observed for aluminum–carbodiimide complexes,¹⁹ thereby facilitating a highly organized metal–ligand–substrate complex. Our model for enantioselectivity places the larger substituent (R_L) in the pseudoaxial position.²⁰ Hydride transfer from the methine carbon of the Al–OⁱPr moiety in **A** via a concerted, six-membered transition state accomplishes the reduction to amide, giving **B** (Scheme 1). Support for this proposal comes from NMR and equivalency studies. A 1:1:1 mixture of (*S*)-BINOL/AlMe₃/2-propanol/**1** in C₆D₆ exhibits a single broad ²⁷Al NMR signal

Scheme 1. Proposed Pathway for the Selective Reduction of *N*-Phosphinoyl Ketimines



at 45 ppm, indicative of a pentacoordinate aluminum species.²¹ Additionally, a downfield shift of the imine's ³¹P resonance from 17 to 22 ppm after exposure to a mixture of BINOL/AlMe₃/2-propanol supports a coordination to the Lewis acidic aluminum center and the resulting loss of electron density at the phosphorus center.²²

Table 3. Ligand Effects in the MSPV Reduction of Ketimine **1**



entry	Al reagent	X equiv of BINOL	conversion ^a (%)	ee ^b (%)
1	AlMe ₃	0	45	0
2	AlMe ₃	1.2 (<i>S</i>)	92	96 (<i>R</i>)
3	AlMe ₃	1.8 (<i>S</i>)	10	<i>c</i>
4	AlMe ₃	2.4 (<i>S</i>)	0	<i>c</i>
5	AlMe ₃	1.2 (<i>R</i>)	93	95 (<i>S</i>)
6	Al(O ⁱ Pr) ₃ ^d	0	55	0

^a Determined by GC at 20 h. ^b Determined by chiral HPLC (Chiralcel OD-H column). ^c Not determined. ^d 10 equiv.

Our proposal allows for an easy prediction of the absolute configuration of the product: (*S*)-BINOL should yield (*R*)-amide, and (*R*)-BINOL would result in the (*S*)-amide, respectively (Table 3, entries 2 and 5). As previously observed for the asymmetric MSPV reduction of ketones,¹¹ a 1:1 BINOL/AlMe₃ complex is optimal for the imine reduction reported herein. Modulating the ligand/metal ratio to 1.5:1 decreases the yield of reaction to only 10% (Table 3, entry 3), and an increase to 2:1 affords no product (Table 3, entry 4). Significantly, preliminary experiments indicate that this reaction is ligand-accelerated:²³ use of 1.2 equiv of AlMe₃ alone yielded only 45% of the amide product, while a 10-fold excess of Al(OⁱPr)₃ yielded only 55% of **11** (Table 3, entries 1 and 6, respectively) under analogous conditions.

In summary, we have disclosed a highly asymmetric MSPV reduction of *N*-diphenylphosphinoylketimines using an inexpensive metal and a readily available chiral ligand.

(17) For an example of the cobalt-catalyzed enantioselective borohydride reduction of aldimines, see: Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura, I.; Ikeno, T.; Yamada, T. *Org. Lett.* **2003**, *5*, 3555–3558.

(18) Enantiomerically pure samples of both (*S*)- and (*R*)-BINOL can be purchased from AB Chem Product List (NJ) for ~\$1.85/g on a kilogram scale.

(19) Rowley, C. N.; DiLabio, G. A.; Barry, S. T. *Inorg. Chem.* **2005**, *44*, 1983–1991.

(20) For a discussion of imine geometry affecting enantioselectivity, see ref 15b.

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While our system is still stoichiometric, it offers exceptional yield and enantioselectivity in the asymmetric reduction of acyclic aliphatic imines, a challenge that has not been met to date. Not only does our protocol greatly expand the utility of the (BINOL)Al^{III} system and asymmetric imine reduction chemistry, it complements the Noyori Ru-based transfer hydrogenation catalyst and the BINAL-H reagent. As a neutral reductant, 2-propanol enables the reduction of imines containing the acid-labile *N*-phosphinoyl protecting group and allows for additional flexibility in synthesis when orthogonal protecting chemistry is often employed.²⁴ Further developments of this reaction and a full mechanistic inves-

(24) The acidic nature of the hydrogen source (HCO₂H·NEt₃) employed in Noyori's ruthenium-based transfer hydrogenation system makes it unsuitable for the reduction of *N*-phosphinoyl imines (see ref 16). We note that 2-propanol was not an effective hydrogen donor in the Noyori imine reductions. Indeed, the reduction of **1** with 2-propanol using 5 mol % of Noyori's cymene diamine Ru^{II} catalyst [(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine](*p*-cymene)ruthenium(II)] proved futile.

tigation are currently being pursued and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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