JOC Article

Ytterbium Acetate Promoted Asymmetric Reductive Amination: Significantly Enhanced Stereoselectivity

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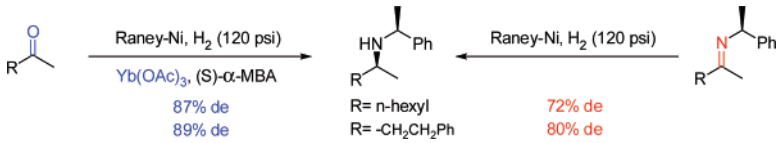

Reductive amination of prochiral unhindered 2-alkanones **1** with (*R*)- or (*S*)-α-MBA in the presence of $Yb(OAc)_3$ (50−110 mol %), Raney-Ni, and hydrogen (120 psi) results in increased diastereoselectivity for the amine products **2** (80−89% de) with good yield (80−87%). The increased de is based on comparison with the best previously reported de's when using (*R*)- or (*S*)-α-MBA, regardless of the strategy employed [stepwise (isolation of ketimines) or one-pot (reductive amination)], reducing agent examined, or achiral Lewis acid or Brønsted acid examined. An in situ *cis*- to *trans*-ketimine isomerization mechanism, promoted by $Yb(OAc)_3$, has been proposed to account for the observed increase in diastereoselectivity and suggests a new entry into the control of ketimine geometry.

Introduction

α-Chiral amines are useful advanced intermediates for alkaloid natural product synthesis and have been successfully incorporated into billion dollar drugs, e.g., several ACE inhibitors and Flomax.[1] Despite their increasing presence in pharmaceutical targets, use as ligands, and recent and extensive exploitation as organocatalysts,[2] a lack of expedient, efficient, and simple methods for their synthesis is evident.[1,3,4] This is exemplified by the fact that at least 40% of all optically active pharmaceutical drugs contain an α-chiral amine moiety, yet 80% of the required syntheses rely on classical resolution methods to obtain the enantiopure amine.[5] This unmet need, especially regarding the synthesis of alkyl−alkyl′ substituted α-chiral amines, continues to be a major challenge and is addressed in this manuscript.

Of the commonly explored strategies for α-chiral amine synthesis,[3] reductive amination[6] holds the advantage of being stepwise efficient[7] and has been recently labeled as a *key green chemistry research area*.[8] Sodium cyanoborohydride and sodium triacetoxyborohydride hold a unique role as useful hydride agents for reductive amination and have been extensively

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(4) A noteworthy and valuable exception is the synthesis of aryl-alkyl substituted α-chiral primary amines via a one-pot enantioselective transfer hydrogenation process for the reductive amination of aryl alkyl ketones, see: Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

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(6) The term reductive amination is sometimes incorrectly associated with the reduction of imines and derivatives thereof. Reductive amination is the one-pot conversion of a ketone to an amine. The term "indirect reductive amination" can be more tersely and accurately described as "imine reduction". For literature pertaining to the origins and definition of reductive amination, see: (a) Emerson, W. S. *Org. React.* **1948**, *4*, 174. (b) Moore, M. L. *Org. React.* **1949**, *5*, 301. (c) *March's Advanced Organic Chemistry*, 5th Ed.; Smith, M. B., March, J., Eds.; John Wiley & Sons, Inc.: New York, 2001; pp 1187−1189.

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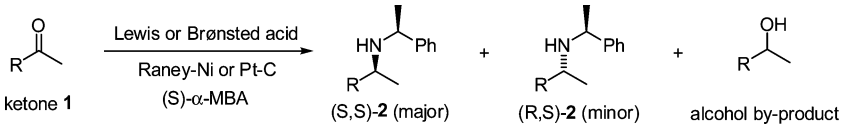
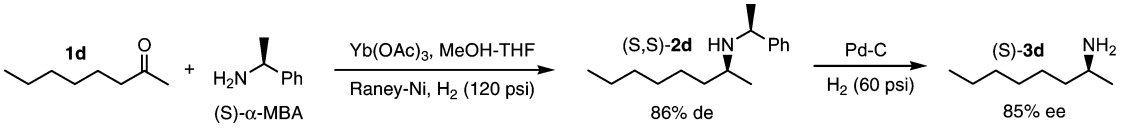
SCHEME 1. Reductive Amination Products of 2-Alkanones with (S)-α-Methylbenzylamine



SCHEME 2. Two-Step Procedure for Producing (2S)-Aminooctane with Enhanced ee



examined and reviewed[9] but cannot be considered as green reagents. More atom efficient is the use of catalytic quantities of a Brønsted acid in combination with hydrogen for reductive amination, this method is routinely practiced by pharmaceutical chemists for achiral carbon−nitrogen bond formation, but is not often reported on. Asymmetric reductive amination studies in these and other laboratories have demonstrated the effectiveness of using stoichiometric quantities of a Lewis acid, e.g., $M(OR)_n$ where M = Ti, Al, or B, and R = Me or ^{i}Pr, instead of a Brønsted acid, for accessing alkyl−alkyl′- or aryl−alkyl-substituted α-chiral primary amines (Scheme 1).[10,11] Regarding enantioselective variants, reductive amination employing molecular hydrogen,[12] transfer hydrogenation,[4] and organocatalytic approaches[13] have recently been demonstrated.

We recently determined[1c] that prochiral ketone substrates of the general structure $R_LC(O)CH_3$ and $R_LC(O)R_S$ allow high de's (87−98%),[14] while substrates $R_MC(O)CH_3$ provide good to high de's (80−93%) when subjected to reductive amination with (*R*)- or (*S*)-α-methylbenzylamine (α-MBA), $Ti(O^iPr)_4$, and Raney-Ni or Pt−C. For straight-chain aliphatic ketones, $R_SC(O)CH_3$,[14] the de's were mediocre (66−74%).[1c,11b] Here, we report on a new asymmetric reductive amination procedure using $Yb(OAc)_3$ (50−110 mol %) that allows increased de (6−15% units) for those ketone substrates, $R_SC(O)CH_3$ and $R_MC(O)CH_3$, that previously only provided mediocre to good de. The enhanced de is based on comparison with the best previously reported de's when using (*R*)- or (*S*)-α-MBA regardless of the strategy employed, stepwise (via isolated ketimines) or one-pot (reductive amination),[6] or the reducing agent examined.[15] Within the field of reductive amination itself, no precedent for enhanced stereoselectivity in the presence of an achiral Lewis acid or a Brønsted acid exists to our knowledge.

Results and Discussion

Stoichiometric Ytterbium Acetate Promoted Reductive Amination (Enhanced de). Our focus on and further exploitation of (*R*)- and (*S*)-α-MBA[16] is partly based on their low cost, as exemplified by their use on an industrial scale for the resolution of some amino acids, e.g., (±)-mandelic acid.[17] We have additionally pursued the use of these chiral ammonia equivalents because the reductive amination products (**2**) can be readily hydrogenolyzed,[1c,15f] allowing enantioenriched α-chiral primary amines (**3**) to be isolated in high overall yield in two steps from prochiral ketones (Scheme 2).

During our investigation of reductive amination reaction conditions that could provide increased rates of reaction and/or stereoselectivity, we examined many row 4 and 5 transition-metal and lanthanide chlorides, acetates, and triflates. Of those, only ytterbium acetate [$Yb(OAc)_3$] allowed significantly increased de with good reaction times. For example, 2-octanone (**1d**), in MeOH, was fully consumed within 8 h providing the secondary amine **2d** in 82% de in the presence of Raney-Ni (Scheme 2). When the solvent was changed to THF, the stereoselectivity increased to 85% de, but 24 h were required to completely consume the 2-octanone starting material. When the binary solvent system of MeOH−THF (1:1) was examined, an 86% de was observed with a fast reaction time of 10 h (Scheme 2 and Table 1, entry 1). We additionally noted that replacing THF, in the MeOH−THF solvent mixture, with toluene, Et_2O, or 1,3-dioxolane provided the same de, but with

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(14) The subscript serves as a generic reference to the steric bulk of the substituent: R_S = small (any straight chain alkyl substituent, but not a methyl group); R_M = medium, e.g. $-CH_2CH_2Ph$ or -*i*-Bu; R_L= e.g. -Ar, -*i*-Pr, -*c*-hexyl.

(15) For advances in the diastereoselective reduction of (*R*)- or (*S*)-α-MBA ketimines, see: (a) Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B. *J. Med. Chem.* **1973**, *16*, 480. (b) Clifton, J. E.; Collins, I.; Hallett, P.; Hartley, D.; Lunts, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670. (c) Eleveld, M. B.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1986**, *51*, 3635−3642. (d) Bringmann, G.; Geisler, J.-P. *Synthesis* **1989**, 608. (e) Marx, E.; El Bouz, M.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1992**, *33*, 4307. (f) Moss, N.; Gauthier, J.; Ferland, J.-M. *Synlett* **1995**, 142. (g) Lauktien, G.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457. (h) Bisel, P.; Breitling, E.; Frahm, A. W. *Eur. J. Org. Chem* **1998**, 729. (i) Gutman, A. L.; Etinger, M.; Nisnevich, G.; Polyak, F. *Tetrahedron: Asymmetry* **1998**, *9*, 4369. (j) Cimarelli, C.; Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2555. (k) Storace, L.; Anzalone, L.; Confalone, P. N.; Davis, W. P.; Fortunak, J. M.; Giangiordano, M.; Haley, J. J., Jr.; Kamholz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L., Jr.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C. *Org. Process Res. Dev.* **2002**, *6*, 54.

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(18) When (*S*)-α-MBA is used as the limiting reagent [(ketone 1.2 equiv and undried $Yb(OAc)_3$ (1.1 equiv)], as shown in Table 1, (±)-2-aminooctanane was consistently observed at 6−7 area % (GC).

TABLE 1. Identification of $Yb(OAc)_3$ for Enhanced Diastereoselectivity−Reductive Amination of 2-Octanone (Scheme 2, Reaction Step 1)[a]

					amine **2d** (Scheme 2)	
entry	additive	time (h)	(S)-α-MBA[b] (%)	2-octanol (%)	yield (%)	de (%)
1	$Yb(OAc)_3$	10	0.7	0.3	90.4	86.1[c]
2	$YbCl_3$	23	77.4	0.0	22.5	66.2
3	$Yb(OTf)_3$	9	-[e]	96.4	3.5	
4	$Ti(O^iPr)_4$[d]	10	2.8	11.4	82.3	67.0
5	$B(O^iPr)_3$[d]	10	14.7	24.4	59.6	71.0
6	$MgSO_4$	12	19	29.3	52.0	70.5
7	4 Å M.S.	12	18.7	28.8	52.5	69.6
8	none	12	24.2	34.6	41.1	70.8
9	NaOAc	23	26.5	43.3	29.7	70.8
10	HOAc	12	4.3	1.0	94.1	72

[a] (S)-α-MBA (2.5 mmol, 1.0 equiv), 2-octanone (1.2 equiv), and an additive (entries 1−5, 9, and 10: 1.1 equiv of additive; entry 6: 5.0 equiv; entry 7: 4.0 wt equiv) were stirred in MeOH (1.0 M) for 30 min at rt, and then THF (final molarity 0.5 M) and Raney-Ni were added and the reaction was pressurized with H_2 (120 psi). All data is based on GC area % analysis. [b] Sum of (S)-α-MBA and ketimine remaining at the indicated time. [c] This result is when $Yb(OAc)_3$ was not vacuum-dried.[18] [d] See ref 19. [e] Not integrated, to emphasize the presence of the dominant alcohol byproduct.

moderately longer reaction times, as did EtOH−THF. Before moving forward with our study we hydrogenolyzed the reductive amination product **2d** to establish the enantiopurity of the primary amine (Scheme 2). Later we found that vacuum drying $Yb(OAc)_3$ allowed the diastereoselectivity to be consistently improved to 87%. This level of diastereoselectivity represents a 15% unit increase in de over the best previously reported for 2-octanone with α-MBA.[11b]

Examination of other simple salts of ytterbium, Yb, demonstrated the significance of having an acetate counterion. For example, when 2-octanone (**1d**) was examined in MeOH, $Yb(OTf)_3$ converted all of the ketone to the corresponding alcohol within 9 h, whereas $YbCl_3$ provided the product in 66% de, but in only 23 area % (GC) after 24 h (Table 1, entries 2 and 3). To probe the possibility that "free" acetate, in solution, had constructively modified the heterogeneous metal surface, the effect of adding NaOAc was examined (Table 1, entry 9). In the event, gross quantities of the alcohol byproduct resulted and a significantly lower product de resulted, making this simplified scenario less likely. Next acetic acid, a commonly used Brønsted acid for reductive amination, was examined, as expected it suppressed alcohol byproduct formation, but provided the secondary amine **2d** in 72% de with the optimized solvent (MeOH). When acetic acid (50, 100, or 200 mol %) was intentionally added to the $Yb(OAc)_3$ reaction described in Table 1 (entry 1), an amine product de of 72% was always noted (data not included in Table 1).

Past speculation regarding the role of Lewis acids in Lewis acid promoted reductive amination has generally relegated them to the level of efficient desiccants for in situ ketimine formation. To study this effect more closely, we examined some traditional desiccants. When $Yb(OAc)_3$ (1.1 equiv) is replaced by $MgSO_4$ (5.0 equiv) or 4 Å molecular sieves (4.0 wt equiv), both vacuum oven dried at 150 °C for 15 h before use, not only are low diastereoselectivities observed (Table 1, compare entries 1, 6, 7), but large quantities of 2-octanone are reduced to the alcohol byproduct. In relation to these results, alcohol byproduct formation could be suppressed when employing $Ti(O^iPr)_4$ (1.25 equiv), but the de remained low (Table 1, entry 4).[19] These combined findings clearly establish $Yb(OAc)_3$ as fulfilling a greater role than that of a simple desiccant.

Useful Substrate Range (Stoichiometric $Yb(OAc)_3$). After further experimentation we established the optimal, in terms of yield and de,[20] protocol as stirring the ketone (limiting reagent), α-MBA (1.1 equiv), and dried $Yb(OAc)_3$[21] in MeOH (1.0 M) for 20−30 min followed by addition of Raney-Ni, as a slurry in THF (final reaction molarity 0.5 M), and pressurization with hydrogen (120 psi) at 22 °C. This general procedure was used for all subsequently described reactions and suppressed the formation of a previously noted byproduct, (±)-2-aminooctane,[18,22,23] to 1−3 area % (GC) when examining 2-octanone.

Examination of the data in Table 2 shows that substrates of the general class $R_SC(O)CH_3$, linear 2-alkanones,[14] are excellent substrates for the new ytterbium based reductive amination method. In particular longer straight chain 2-alkanones, e.g., 2-octanone (**1d**) and 2-hexanone (**1e**), show dramatic improvements in de, 15% and 14%[24] unit changes respectively, with

(19) Note that in this initial study (Table 1), (*S*)-α-MBA was the limiting reagent. The optimal procedures defined for titanium-, aluminum-, and boron-based reductive aminations require the ketone as the limiting reagent and reliably provides a de of 72% for 2-octanone in THF (without MeOH); see ref 1c. Under those conditions, $Ti(O^iPr)_4$ (1.25 equiv) suppresses alcohol formation below 3%. In general, $B(O^iPr)_3$ is less efficient at suppressing alcohol byproduct formation; use of more equivalents of $B(O^iPr)_3$ (>1.25 equiv) is then helpful.

(20) All quoted yield data is after chromatography. Alternatively, these compounds can be isolated in near-qualitative purity (GC and ^1H NMR) without the need for flash chromatography using the acid/base workup procedure found in the general Experimental Section. Note that during the ammonium chloride washing, the small excess of (*R*)- or (*S*)-α-MBA preferentially dissolves in the aqueous layer, while the desired and more lipophilic amine product **2** preferentially dissolves in the organic layer. Note: This has not been tested for product **2f**. All amine products **2** should be considered as volatile (<15 carbons) or semivolatile (<18 carbons) under high vacuum drying or under prolonged rotary evaporation; HCl salt formation (add ethereal HCl) is required for high vacuum drying.

(21) We noted after using several bottles of $Yb(OAc)_3$, which is sold and described as a semihydrated form (Sigma-Aldrich catalog no. 544973), that it was sometimes free flowing while other bottles from the same lot were not. As a consequence, 10 g quantities of $Yb(OAc)_3$ were high vacuum dried to constant weight at 80 °C (12 h), and $Yb(OAc)_3$ treated in this way was used for the optimal results shown here. In this manuscript, "dry $Yb(OAc)_3$" means dried as just stated. The dried $Yb(OAc)_3$ could be stored in a dry screw cap glass bottle at room temperature, and this container could be repeatedly opened to the atmosphere (at least 6 times without detrimental effect) and the desired quantity of $Yb(OAc)_3$ weighed out without the need for a glovebox. In this way, constant and repeatable results were always observed.

(22) Curiously, the noted byproduct 2-aminooctane was a racemate (GC analysis of the trifluoroacetamide derivative), excluding the possibility that it originated from a sequential reductive amination of (*S*)-α-MBA with 2-octanone followed by in situ hydrogenolysis of the product **2d**. It also did not originate from the in situ hydrogenolysis of (*S*)-α-MBA (forming ammonia and ethylbenzene), followed by reductive amination of ammonia with 2-octanone. This is known because ethylbenzene (relative to an authentic reference standard) was never noted (GC) even when taking care to work up the reaction at 0 °C with aqueous $NaHCO_3$/EtOAc to avoid evaporation of ethylbenezene (bp = 136 °C). While [1,3]-proton shifts of imines are known, they are to our knowledge only accomplished under the presence of a strong base; see ref 23. If a [1,3]-proton shift of the initially formed imine occurred, followed by in situ hydrolysis, 2-aminooctane and acetophenone would result. When 2-octanone (1.0 equiv), (*S*)-α-MBA (1.1 equiv), and $Yb(OAc)_3$ (1.1 equiv) were added to THF−MeOH (standard reaction conditions) and the mixture stirred in the absence of Raney-Ni and H_2, a very small quantity of a new compound (<2 area %) with very similar retention time to acetophenone (as compared to an authentic sample) was noted. No further studies regarding the origin of 2-aminooctane formation were pursued and as stated earlier high vacuum drying of $Yb(OAc)_3$ suppressed 2-aminooctane formation below 3 area % (GC).

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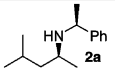
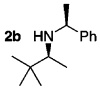
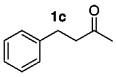
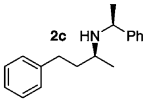
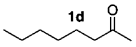
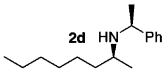
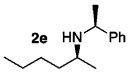
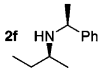
TABLE 2. Ketone Substrate Breadth for Enhanced Diastereoselectivity[a]

entry	2-alkanone **1**	amine product **2**	yield (%)[b]	*de* (%)[c]	change in *de* (%)[d]
1			78	94	1
2			77	92	0[e]
3			87	89	9
4			86	87	15
5			82	85	14
6			80	80	6

[a] Ketone (2.5 mmol, 1.0 equiv), dried $Yb(OAc)_3$ (1.1 equiv),[21] (*S*)-α-methylbenzylamine (1.1 equiv), Raney Ni, H_2 (120 psi), MeOH−THF (1:1) 0.50 M, 22 °C, 12 h. [b] Isolated yield of both diastereomers after chromatography. [c] Determined by GC analysis of crude product **2**. [d] Percent unit change in de compared to the best previously reported de.[1c,11b,15b] [e] Pinacolone is a Pt−C substrate and requires 22 h at $T = 50$ °C.

good isolated yield (Table 2, entries 4 and 5) vs the best previously reported methods.[1c] For this study, we additionally synthesized and isolated the *N*-(S)-α-MBA ketimine of 2-octanone, its reduction with Raney-Ni/H_2 in THF−MeOH (1:1) provided **2d** in 64% de. The short-chain 2-butanone (**1f**) showed a smaller but consistent and significant 6% unit increase in de vs the best previously reported result ($Ti(O^iPr)_4/CH_2Cl_2$/Raney-Ni: 74% de).[1c]

Comparison of substrates that can be loosely qualified as having a medium-sized R substituent residing on the 2-alkanone carbonyl, $R_MC(O)CH_3$,[14] help define the boundary substrates for enhanced stereoselectivity. For example when the γ-branched benzylacetone (**1c**) was examined, a 9% unit increase in de was observed vs the previous best reported methods (Table 2, entry 3).[1c,15b] For the β-branched isobutyl methyl ketone (**1a**), no improvement in stereoselectivity (1% increase) was noted (Table 2, entry 1). When α-branched 2-alkanones, e.g., isopropyl methyl ketone or cyclohexyl methyl ketone, are subjected to reductive amination with $Ti(O^iPr)_4$ the product is formed with high de (>98% de);[1c] no improvement was noted when using $Yb(OAc)_3$.[25,26]

Catalytic Lewis Acid-Promoted Reductive Amination. Encouraged by our results with stoichiometric quantities of $Yb(OAc)_3$ and aware of the fact that catalytic quantities of a Lewis acid have not been previously reported for promoting efficient reductive amination, we further investigated this point. When 2-octanone was examined, the use of 80 mol % of $Yb(OAc)_3$ allowed the same 87% de to be achieved as when 110 mol % was used, and interestingly, the use of 50 mol % of $Yb(OAc)_3$ was equally effective (86% de). Lowering the mol % of $Yb(OAc)_3$ below 40% led to a rapid deterioration in the diastereoselectivity, such that when 10 mol % of $Yb(OAc)_3$ was used no enhancement in stereoselectivity could be expected. At 20 mol % loading, a 79% de was observed, and repetition of this experiment in the presence of 4 Å molecular sieves (4 wt equiv) provided no additional benefit.

When less than 10 mol % of $Yb(OAc)_3$ was employed, greater than 3 area % (GC) of the alcohol byproduct was noted; thus, we chose 10 mol % to determine the isolated yields for a broad range of substrates (Table 3).[27] Before doing so, we investigated a large variety of transition-metal, lanthanide, and metalloid halides, acetates, alkoxides, and sulfonates for their ability to allow fast and high yielding reductive amination reactions to occur. By doing so, we were able to further identify $Ce(OAc)_3$

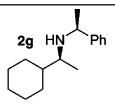
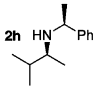
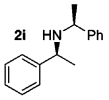
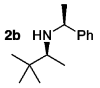
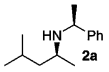
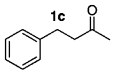
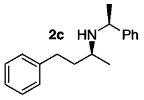
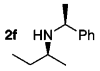
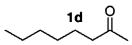
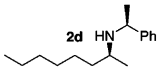
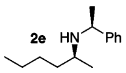
(24) 2-Hexanone is quoted as having a 14% unit increase in de (71% vs 85% de); this is based on comparison with entry 9 of Table 3 of this manuscript. If compared to our earlier findings, ref 1c, the increase would be 19% (66% vs 85 % de). In ref 1c, we speculate that the low de of 2-hexanone is not explainable based on the 2-octanone and 2-butanone results shown therein; thus, we believe 14% more accurately reflects the true difference.

(25) Ketone substrates with an α-quaternary carbon do not undergo reductive amination with Raney-Ni, even under forcing conditions; instead, Pt−C is the catalyst of choice for this class of prochiral ketones. Examination of pinacolone (**1b**) with $Yb(OAc)_3$/Pt-C/H_2 provided a consistent 92% de (Table 2). For this Pt substrate, there is no change in de verses the previously best reported method; see ref 15f.

(26) Examination of aryl alkyl ketones, e.g., acyclic acetophenone or cyclic benzosuberone, or a non-2-alkanone, e.g., isopropyl *n*-propyl ketone, proved problematic. Acetophenone required higher temperature, 60 °C with 120 psi of H_2, and produced the product in 92% de but with large amounts of the corresponding alcohol noted (~20 area %, GC). For benzosuberone and isopropyl *n*-propyl ketone, repeated attempts to obtain the intended product by heating and/or increasing the hydrogen pressure failed. For these substrates, the desired products can be produced in good yield and de using $Ti(O\text{-}i\text{-}Pr)_4$ instead of $Yb(OAc)_3$; see ref 1c.

(27) Regarding aryl alkyl ketones, acetophenone (Table 3, entry 3) was sluggish to react even at 50 °C and 432 psi (30 bar) of hydrogen, with isolated yields varying between 55−65% and concomitant alcohol byproduct formation always noted. Examination of 1-phenylbutanone at 50 °C and 432 psi (30 bar) of hydrogen only allowed ~20 area % (GC) of the expected product to form after 24 h. Benzosuberone (cyclic aryl alkyl ketone) and isopropyl *n*-propyl ketone, under similar forcing conditions (50 °C, 580 psi (40 bar) H_2, >24 h), showed these sterically challenging substrates could not be converted to the desired product with catalytic quantities of $Yb(OAc)_3$.

TABLE 3. 10 mol % Yb(OAc)$_3$ Catalyzed Reductive Amination: Substrate Breadth[a]

entry	ketone **1**	secondary amine **2**	yield %[b]	de %[c]
1			81	98
2			78	98
3			63	94
4[d]			78	92
5			79	92
6			87	80
7			82	79[e]
8			83	72
9			82	71

[a] Ketone (2.5 mmol), dried Yb(OAc)$_3$ (10 mol %),[21] (*S*)-α-methylbenzylamine (1.1 equiv), Raney Ni, 0.50 M (MeOH−THF, 1:1), 12 h. Entries 1−4: T = 50 °C, H_2 pressure = 290 psi (20 bar); entry 5: T = 50 °C, H_2 pressure = 120 psi (8.3 bar), entries 6−9: T= 22 °C, H_2 pressure = 120 psi (8.3 bar). [b] Isolated yield of both diastereomers after chromatography; also see ref 20. [c] Determined by GC analysis of the crude product. [d] Pt−C was used instead of Raney Ni, T = 50 °C, H_2 pressure = 120 psi. [e] Non-Yb(OAc)$_3$ based methods provide 74% de.

(15 mol %) and Y(OAc)$_3$ (15 mol %)[28] as consistently providing results similar to Yb(OAc)$_3$ (10 mol %), regarding reaction time, yield, and diastereoselectivity for the reductive amination of 2-octanone (**1d**) with (*S*)-α-MBA.[29] Use of stoichiometric Ce(OAc)$_3$ or Y(OAc)$_3$ did not provide enhanced de or any other added benefit over those reactions examined at the 15 mol % level.

Finally, in contrast to earlier industrial findings regarding the beneficial use of 5 mol % of thionyl chloride for promoting ketimine formation,[30] replacement of the Lewis acid by thionyl chloride led to the amine product **2d** in 50% de. The use of phosphorus oxychloride has not been previously reported on and we found its use to be beneficial at 10 mol % (72% de), but upon completion of the reductive amination, the alcohol byproduct was observed in ∼4 area % (GC).[31]

Stoichiometric and Catalytic Brønsted Acid-Promoted Reductive Amination. Brønsted acids are well-known for promoting reductive amination, but an overview of useful Brønsted acids is, to our knowledge, not available in the primary literature. The Table 4 data shows that 20 mol % of acetic acid, trichloroacetic acid, or formic acid is optimal for the reductive amination of 2-octanone with α-MBA. The use of 5 mol % of AcOH had the detrimental effect of allowing significant alcohol byproduct formation (>5 area %, GC). The use of stoichiometric quantities of acetic acid, trichloroacetic acid, or formic acid had no detrimental effect on the reaction rate or yield (GC) and consistently provided secondary amine **2d** in 72% de (Table 4), in contrast to Yb(OAc)$_3$ (Table 2, 87% de).

(28) Y(OAc)$_3$ and Ce(OAc)$_3$ were dried as indicated in ref 21. Sigma-Aldrich catalog nos.: Y(OAc)$_3$ 326046, Ce(OAc)$_3$ 529559.

(29) A second and larger group of Lewis acids, In(OAc)$_3$, Sc(OAc)$_3$, CuOAc, Er(OAc)$_3$, Gd(OAc)$_3$, Dy(OAc)$_3$, AgOAc, Zn(OAc)$_2$, and Cd(OAc)$_2$, emerged as being useful (15 mol %), but always provided larger quantities of the alcohol byproduct, typically 5−15 area % by GC analysis. Use of the corresponding chlorides or triflates of the same elements (15 mol %) proved detrimental, with >25 area % of the alcohol byproduct forming in most instances. Exceptions to this general observation were noted for Bi(OTf)$_3$, AgCl, ScCl$_3$, and scandium hexafluoroacetylacetone, which provided 5−15 area % of the alcohol byproduct and/or observably longer reaction times than Yb(OAc)$_3$ (10 mol %), Y(OAc)$_3$ (15 mol %), or Ce(OAc)$_3$ (15 mol %). Initially, 15 mol % of the metalloids Bi(OAc)$_3$ and Sb(OAc)$_3$ were included as useful as Y(OAc)$_3$ or Ce(OAc)$_3$, but they smelled of AcOH and were thus dried to a constant weight. Upon reexamination, dried Bi(OAc)$_3$ and Sb(OAc)$_3$ proved uninteresting, implying that coexisting AcOH had catalyzed the earlier reactions.

(30) Farina, V.; Grozinger, K.; Müller-Bötticher, H.; Roth, G. P. Ontazolast: The Evolution of a Process. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker, Inc.: New York, 1999; pp 107−124.

(31) An isolated yield was not determined for the reductive amination reaction catalyzed by phosphorous oxychloride.

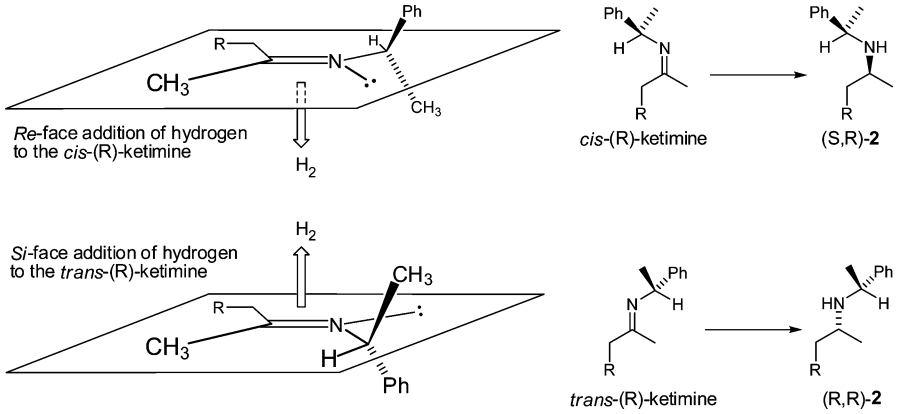


FIGURE 1. Nitrogen−benzylic carbon bond rotamers responsible for hydrogen addition to *cis*- and *trans*-*N*-α-MBA ketimines.

TABLE 4. Brønsted Acid Based Reductive Amination of 2-Octanone with (S)-α-MBA[a]

entry	Brønsted acid (20 mol %)	2-octanone remaining (area %)	alcohol formed (area %)[b]	de[b]
1	acetic acid	1	2	72
2	trifluoroacetic acid		22.3	71
3	trichloroacetic acid	1	2.1	72
4	formic acid		2.7	71
5	oxalic acid	1.7	24	73
6	thiophenol	51.8	3.5	26
7	phenol		29	70

[a] 2-Octanone (2.5 mmol), Brønsted acid (20 mol %), (*S*)-α-methylbenzylamine (2.75 mmol), Raney Ni, 0.50 M (MeOH), 12 h, $T = 22$ °C, H_2 pressure = 120 psi (see the Supporting Information). [b] Determined by GC analysis at 12 h.

A different product profile was noted for strong mineral acids and the very acidic trifluoroacetic acid. For example, when using stoichiometric or catalytic (5 or 10 mol %) quantities of 12 N HCl or 18 M H_2SO_4, *p*-TsOH, or trifluoroacetic acid in MeOH, high alcohol byproduct formation was always noted (15−30 area %, GC).[32] Regardless of the low yield of **2d**, when using these strong Brønsted acids, the product de ranged from 70 to 72% for 2-octanone **1d**.

Regarding the optimal solvent for Brønsted acid based reductive amination, MeOH and EtOH allowed fast reactions, e.g., with AcOH (20 mol %) only 8 h was required. Using the combination of THF−MeOH (which was optimal for the earlier discussed Lewis acids) slowed down the reaction (12 h). Use of THF as the sole solvent for AcOH (20 mol %) further suppressed the reaction rate such that 30−45% of the ketone consistently remained after 24 h of reaction (22 °C, 120 psi H_2).[33] By contrast, the stoichiometric and catalytic Lewis acid promoted reactions in THF were complete at 24 h under otherwise identical reaction conditions. This noted difference in protic vs aprotic reaction solvent profile may allow the future use of substrates containing acid labile functional groups or having restricted solubility.

Finally, acetic acid (20 mol %) was examined for its ability to affect efficient reductive amination in dry MeOH, and representative ketones from Table 3 were chosen. 2-Octanone **1d** (83% isolated yield, 72% de, $T = 22$ °C, 120 psi (8.0 bar) H_2), isobutyl methyl ketone **1a** (80% isolated yield, 92% de, $T = 50$ °C, 120 psi (8.0 bar) H_2), cyclohexyl methyl ketone **1g** (82% isolated yield, 98% de, $T = 50$ °C, 290 psi (20 bar) H_2), and acetophenone **1i** (55% isolated yield, 93% de, $T = 50$ °C, 435 psi (30 bar) H_2) provided very similar reaction rates, isolated yield, and the same de data as the optimal catalytic Lewis acids [$Yb(OAc)_3$ (10 mol %), $Y(OAc)_3$ (15 mol %), and $Ce(OAc)_3$ (15 mol %)] but never showed the enhanced diastereoselectivity possible when using 50−110 mol % $Yb(OAc)_3$ (Tables 2 and 3).[34]

Basic Stereochemical Considerations. Figure 1 provides a working model of the low energy conformers of the *cis*- and *trans*-ketimines influencing facial selectivity during the addition of hydrogen to *N*-α-MBA ketimines. The models are consistent with the major amine diastereomer formed (either *S*,*S* or *R*,*R* depending on the starting enantiomer of α-MBA) and are in accordance with the well-established concept of allylic 1,3-strain[35] and earlier proposed models.[15c,i] Contrary to this model, it has been previously suggested that the reductive amination of an α-keto ester with α-MBA may involve a rotamer (about the nitrogen-benzylic carbon bond) with the phenyl ring of α-MBA coplanar to the ketimine double bond.[36] The idea is appealing because of the well described affinity of π bonds for heterogeneous hydrogenation catalyst surfaces,[37] but examination of the two possible *trans*-ketimine rotamers (not shown), with a coplanar phenyl group relative to the ketimine double bond, shows one suffering from high allylic 1,3-strain[35] (prominent phenyl group steric crowding with the methyl group attached to the carbonyl carbon of the ketimine) while the other rotamer is less encumbered (1,2-strain from the electron pair

(32) It should be noted that the strong Brønsted acids mentioned here may act as good acid catalysts for the reductive amination of ketone/amine combinations that are less sterically congested as compared to the ketone/α-MBA combinations shown here.

(33) It is important to note that little or no alcohol byproduct formation was noted during these incomplete reactions in THF.

(34) When using 20 mol % AcOH with the sterically hindered ketone substrates benzosuberone, 1-phenylbutanone, or isopropyl *n*-propyl ketone, the effect of temperature (22−50 °C) and hydrogen pressure [120−580 psi (8−40 bar)] were independently and then concurrently examined; only 1-phenylbutanone provided the desired product and then only in very low yield (20−25 area %, GC) after >24 h of reaction. For these types of substrates, the only effective reductive amination conditions are those employing stoichiometric quantities of $Ti(O^iPr)_4$; see ref 1c.

(35) (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Lee, K. W.; Hwang, S. Y.; Kim, C. R.; Nam, D. H.; Chang, J. H.; Choi, S. C.; Choi, B. S.; Choi, H.-W.; Lee, K. K.; So, B.; Cho, S. W.; Shin, H. *Org. Process Res. Dev.* **2003**, *7*, 839.

(36) Siedlaczek, G.; Schwickardi, M.; Kolb, U.; Bogdanovic, B.; Blackmond, D. G. *Catal. Lett.* **1998**, *55*, 67.

(37) (a) Kraynov, A.; Suchopar, A.; D'Souza, L.; Richards, R. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1321. (b) Bürgi, T.; Baiker, A. *Acc. Chem. Res.* **2004**, *37*, 909. (c) Studer, M.; Blaser, H.-U.; Exner, C. *Adv. Synth. Catal.* **2003**, *345*, 45.

TABLE 5. Early Reaction Progress: Stereochemical Outcome for the Reductive Amination of 2-Octanone (1d)[a]

						amine product **2d**	
entry	additive	time (h)	(S)-α-MBA[b] (%)	2-octanone (%)	2-octanol (%)	yield (%)	de (%)
1	$Yb(OAc)_3$	1[c]	18.1	6.5	0.5	73.9	87.1
		3[d]	12.5	2.5	1.0	81.5	87.2
2	$Ti(O^iPr)_4$	1	43.9	7.9	0.63	47.6	67.0
		3	8.5	4.0	2.1	85.4	67.0
3	none	1	47.1	10.5	16.6	25.8	72.0
		3	29.2	1.1	27.6	42.2	72.1

[a] 2-Octanone (2.5 mmol, 1.0 equiv), (*S*)-α-MBA (1.1 equiv), and $Yb(OAc)_3$ or $Ti(O^iPr)_4$ (1.1 equiv) were stirred in MeOH (1.0 M) for 90 min at rt, and then THF (final molarity 0.5 M) and Ra−Ni (100 wt %) were added and the reaction was pressurized with H_2 (8.3 bar/120 psi). All data is based on GC area % analysis. [b] Sum of (*S*)-α-MBA and ketimine remaining. [c] 1.0 area % of (±)-2-aminooctane was noted. [d] 2.5 area % of (±)-2-aminooctane was noted.

TABLE 6. In Situ Ketimine Formation Study: 2-Octanone and (S)-α-MBA[a]

	ketimine area % (GC analysis)		
time (min)	no additive	$Ti(O^iPr)_4$ (1.25 equiv)	$Yb(OAc)_3$ (1.1 equiv)
30	16	38	<3
90	33	40	<3

[a] 2-octanone (1.0 equiv), (S)-α-MBA (1.1 equiv), and the indicated additive were added to anhydrous MeOH (1.0 M).[39] All aliquots were worked-up with saturated aq $NaHCO_3$/EtOAc at the indicated times.

of the ketimine nitrogen and one of the ortho hydrogens of the phenyl ring) but leads to the formation of the wrong amine product diastereomer. It is therefore unlikely that the phenyl ring of an *N*-α-MBA ketimine is adsorbed to the surface of a heterogeneous hydrogenation catalyst at the time of hydrogen addition.

Mechanistic Considerations: Enhanced Stereoselectivity with $Yb(OAc)_3$. Regarding reductive amination in general and the reduction of isolated *N*-α-MBA ketimines, no precedent exists for obtaining enhanced product diastereoselectivity through the use of an achiral Lewis acid or Brønsted acid. Experiments were thus designed to probe the origin of the enhanced diastereoselectivity.

Reductive amination of 2-octanone with $Ti(O^iPr)_4$ or $Yb(OAc)_3$ requires 12 h for complete consumption of the ketone to occur, and examination of the reaction at 1 and 3 h showed the diastereoselectivity of the product to be fully consistent with that found at the end of the reaction (Table 5).[38] These results suggest that one mechanism is operating throughout the reaction period but did not provide further insight into the origin of the enhanced diastereoselectivity.

Because the cis/trans ratio of diastereomeric *N*-α-MBA ketimines is the major parameter influencing the de of the product, we next examined the progress of in situ ketimine formation. GC analysis of a mixture of 2-octanone and (*S*)-α-MBA after 30 min with no additive or with $Ti(O^iPr)_4$ (1.25 equiv) provided a similar area % of the ketimine, but interestingly $Yb(OAc)_3$ never showed appreciable amounts (<3 area %) of the ketimine (Table 6). Attempts to force greater quantities of the ketimine to form in the presence of $Yb(OAc)_3$, e.g., by extending the reaction time to 12 h, failed.

The lack of ketimine accumulation in the presence of $Yb(OAc)_3$ raised the possibility that the *N*-α-MBA ketimine was forming in situ, but subsequent Lewis acid−base pair formation with $Yb(OAc)_3$ made it more susceptible to hydrolysis upon workup, even under the mild conditions of aq $NaHCO_3$/EtOAc. To experimentally support this, we synthesized the *N*-α-MBA ketimine of 2-octanone (Dean−Stark trap, see the Experimental Section), added MeOH (anhydrous)[39] and an equivimolar quantity of $Yb(OAc)_3$ (110 mol %). After 30 min, the mixture was worked up (aq $NaHCO_3$/EtOAc), and again no ketimine (6 area %, GC) was noted, instead the ketone and amine were found. This result combined with the fact that reductive amination is possible in the presence of $Yb(OAc)_3$ strongly suggests that ketimine formation can and does occur in the presence of $Yb(OAc)_3$. Unfortunately, the labile nature of the ketimine in the presence of $Yb(OAc)_3$ rules out the possibility of determining the origin of the enhanced de through comparison of the cis/trans ketimine ratios when no additive or $Ti(O^iPr)_4$ is present vs when $Yb(OAc)_3$ is present.[40]

Taking the above facts into consideration, it seemed probably to us that the in situ generated *trans*- and *cis*-ketimine mixture was being enriched to one having greater *trans*-ketimine representation before hydrogenation occurred. This would be possible if $Yb(OAc)_3$ was capable of isomerizing some of the *cis*-ketimine to the *trans*-ketimine. To examine this possibility, we dissolved the *N*-(*S*)-MBA ketimine of 2-octanone, isolated after Dean−Stark trap synthesis, in MeOH (anhydrous),[39] and stirred it for 30 min[41] in the presence of 110 mol % of $Yb(OAc)_3$ at 22 °C before adding Raney-Ni (THF slurry) and pressurizing with hydrogen (120 psi). At 12 h, no ketimine remained, the reaction profile was clean, and an amine product de of 86% was noted for amine **2d**. This high de for ketimine reduction correlates very closely with that observed during the reductive amination of 2-octanone with (*S*)-α-MBA in the presence of $Yb(OAc)_3$ (87% de) and strengthens the possibility that an in situ *cis*- to *trans*-ketimine isomerization is occurring.[42] Treatment of the same ketimine under identical reaction

(38) The Table 5 study employed the optimal reaction conditions (ketone limiting reagent), when the same study was performed, albeit using (*S*)-α-MBA as the limiting reagent with excess ketone (1.2 equiv), trivial changes in the Table 5 area % numbers were noted.

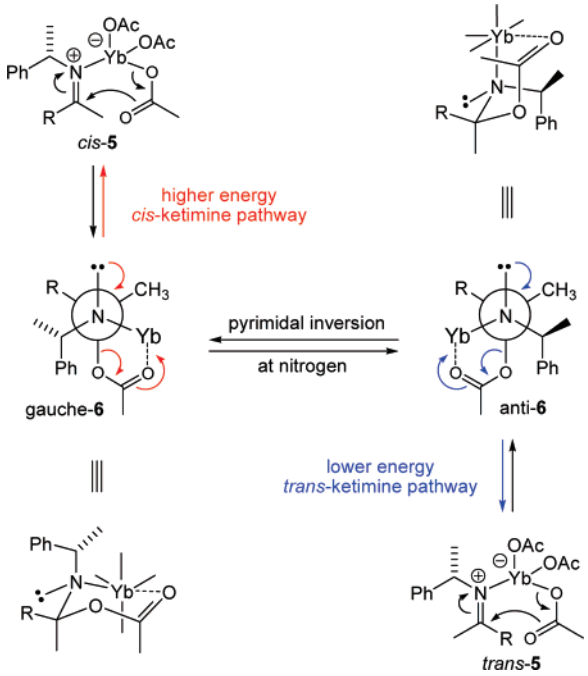
(39) Note the optimal reaction conditions call for stirring the ketone, amine, and $Yb(OAc)_3$ for 20−30 min in MeOH (1.0 M), followed by the addition of Raney-Ni (as a slurry in THF, final reaction molarity 0.5) and immediate pressurization with hydrogen.

(40) In our hands, ^1H NMR experiments of the ketone, α-MBA, and $Yb(OAc)_3$ in CD_3OH proved unhelpful due to the broadening of resonance patterns. The broadening is likely due to the influence of an NMR active isotope of Yb which is paramagnetic. It should be noted that these mixtures are turbid and attempts to filter them and then record the NMR spectrum also failed to provide useful spectroscopic data.

(41) Extending the stirring time from 30 min to 12 h, before the onset of hydrogenation, resulted in the same de.

(42) We also examined the effect of replacing MeOH with THF, but the de dropped to 77%. This can be readily explained by the low observed solubility of $Yb(OAc)_3$ in the THF mixture containing the *N*-(*S*)-MBA ketimine of 2-octanone, allowing the back round reaction to occur and showing the importance of having MeOH as a cosolvent.

SCHEME 3. Proposed Mechanism for in Situ Ketimine Isomerization during Reductive Amination



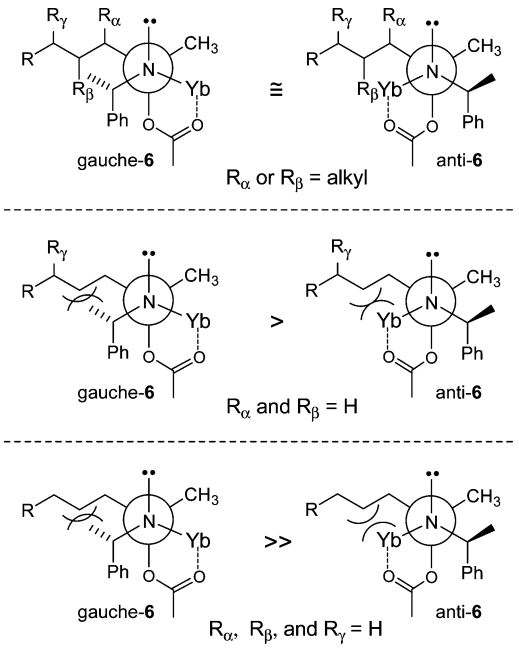


FIGURE 2. Speculative relative free energy differences for branched and nonbranched 2-alkanones.

conditions, albeit without $Yb(OAc)_3$, resulted in an amine product de of 64%.

Outlined in Scheme 3 is a proposed mechanism for ketimine isomerization occurring during reductive amination. It relies on in situ ketimine formation (not shown) followed by Lewis acid−base pair formation between the *cis*- and *trans*-ketimines and $Yb(OAc)_3$ (Scheme 3, *cis*-**5**). Intramolecular attack at the electrophilic carbonyl carbon of the iminium ion by the acetate ligand of ytterbium would proceed via a six-membered transition state forming an oxygen-acetylated hemiaminal (*gauche*-**6**). Pyrimidal inversion at nitrogen is a low energy process which readily occurs at room temperature and for *gauche*-**6** would be further driven by relief of the steric crowding arising from the gauche relationship between the "α-methylbenzyl" substituent on the nitrogen atom and the "R" substituent of the former carbonyl carbon of the ketimine. Nitrogen inversion of *gauche*-**6** would provide *anti*-**6** (Scheme 3), allowing an anti-relationship to exist between the "α-methylbenzyl" substituent of nitrogen and the "R" substituent of the former carbonyl carbon; this conformation also allows an antiperiplanar arrangement to exist between the nitrogen lone pair and the acetate leaving group, allowing facile elimination of acetate and *trans*-ketimine formation (*trans*-**5**).

An explanation for why straight-chain 2-alkanones (e.g., 2-octanone **1d**) and γ-branched 2-alkanones (e.g., benzylacetone **1c**) are good substrates for the method, while α- and β-branched 2-alkanones are not, can be rationalized by more closely examining the "R" substituent of the two Newman projections (gauche-**6** and anti-**6**) shown in Scheme 3. Experimentally, it is known that no improvement in diastereoselectivity is noted for α- or β-branched 2-alkanones when using $Yb(OAc)_3$. This implies that there is not a significant energetic difference between the gauche steric crowding arising from the "α-methylbenzyl" substituent on the nitrogen atom and the "R" substituent of the former carbonyl carbon (Figure 2, *gauche*-**6**, R_α or R_β = alkyl) vs the steric crowding experienced when the "ytterbium" substituent of nitrogen is gauche to the "R" substituent of the former carbonyl carbon (Figure 2, *anti*-**6**, R_α or R_β = alkyl). Enhanced diastereoselectivity is noted for γ-branched 2-alkanones (Figure 2, R_α and R_β = H) and nonbranched 2-alkanones (Figure 2, R_α, R_β, R_γ = H) suggesting that for these ketone substrates Newman projection *gauche*-**6** is higher in energy than *anti*-**6**. This relative free energy difference would be expected to drive *cis*- to *trans*-ketimine isomerization in the presence of $Yb(OAc)_3$.[43−45]

Key Findings for Reductive Amination with α-MBA. This study, and our earlier ones, complete a body of research regarding the reductive amination of prochiral ketones with (*R*)- or (*S*)-α-MBA (1.1 equiv) under the influence of an optimal achiral Lewis acid or Brønsted acid. Comparison of the de's of the reductive amination products **2** when using $Ti(O^iPr)_4$ (stoichiometric) or catalytic Lewis acids [$Yb(OAc)_3$ (10 mol %), $Y(OAc)_3$ (15 mol %), or $Ce(OAc)_3$ (15 mol %)], or Brønsted acids, show them to be equal. Furthermore, if (*R*)- or (*S*)-α-MBA ketimines are synthesized, isolated, and reduced, the same de is noted as when the above-noted Lewis or Brønsted acid catalysts are used for reductive amination of the same ketone

(43) The origin of the difference in relative free energy for the Newman projections can be further rationalized by noting that the "α-methylbenzyl" substituent of nitrogen produces a very large steric volume in the immediate vicinity of nitrogen, while the ytterbium−nitrogen bond will be expected to be longer than the benzylic carbon−nitrogen bond of the "α-methylbenzyl" substituent and thereby reduce the immediate steric volume next to nitrogen. The conclusion, based on the observed substrate de, is that regardless of the level of branching within the "R" substituent (Scheme 3), there is always a high degree of steric crowding when the "α-methylbenzyl" substituent is gauche to it (Figures 2, gauche-**6**). This would not always be the case when comparing the steric crowding of the "R" substituent with a gauche positioned ytterbium. Thus "R" substituents having only γ-branching might be expected to have medium steric crowding with a gauche ytterbium atom (Figure 2, compare gauche-6 and anti-6 when R_α and R_β = H), while nonbranched "R" substituents would have low (relative) steric crowding in relation to a gauche positioned ytterbium atom (Figure 2, compare *gauche*-**6** and *anti*-**6** when R_α, R_β, R_γ = H). These considerations would support the possibility of *cis*-ketimine to *trans*-ketimine isomerization for γ-branched and straight-chain 2-alkanones and thereby their enhanced product de, while at the same time explain why α- and β-branched 2-alkanones would not provide enhanced product de.

starting material with (*R*)- or (*S*)-α-MBA. In contrast to these stereochemical trends γ-branched and nonbranched 2-alkanones, e.g., benzylacetone (**1c**) and 2-octanone (**1d**), respectively, undergo reductive amination in the presence of $Yb(OAc)_3$ (50−110 mol %) providing enhanced diastereoselectivity with good yield. Finally, failure to use the correct acid (Lewis or Brønsted) during reductive amination, or no acid at all, results in high alcohol byproduct formation.

Conclusion

Strategies for α-chiral amine synthesis employing isolated ketimines or enamines are stepwise long and can suffer from lower overall yield because of mediocre ketimine or enamine yield forming steps, as previously commented on.[46] This problem can be alleviated by using a reductive amination strategy as outlined here, and when followed by hydrogenolysis allows enantioenriched primary amine synthesis in good to high overall yield in two reaction steps from prochiral ketones.

To our knowledge ytterbium acetate has not been previously investigated for influencing the double bond geometry of imines or enamines and the use of a ytterbium salt for reductive amination has no prior precedent. The speculative mechanism elaborated on here suggests that a $Yb(OAc)_3$-promoted *cis*- to *trans*-ketimine isomerization pathway may be operative and responsible for the enhanced product de noted for γ-branched and straight-chain 2-alkanones.

Experimental Section

General Procedure: Stoichiometric $Yb(OAc)_3$ (Enhanced de). In a dry reaction vessel, $Yb(OAc)_3$ (0.96 g, 2.75 mmol, 1.1 equiv)[21] was added and subsequently evacuated under high vacuum for 5 min before flooding with nitrogen, anhydrous MeOH (2.5 mL, 1.0 M) was then added. To this solution a prochiral ketone **1** (2.5 mmol, 1.0 equiv) and (*S*)-α-methylbenzylamine (0.35 mL, 2.75 mmol, 1.1 equiv) were added and subsequently stirred at room temperature for 20−30 min. A THF slurry of Raney-Ni (100 wt % based on the ketone, triturated with EtOH (×3) and then with anhydrous THF (×3) before addition) was transferred to the reaction mixture using 2.5 mL of anhydrous THF (final molarity of reaction solution is 0.5 M) and the reaction vessel pressurized at 120 psi (8.3 bar) of hydrogen. After being stirred for 12 h at 22 °C, <3 area % of the ketone and ketimine intermediate remained, GC), the reaction mixture was diluted with MeOH (10 mL) and filtered through a bed of Celite and the Celite subsequently washed with MeOH (3 × 10 mL). The combined filtrate was then evaporated to dryness (rotary evaporate at ≤25 °C for short periods due to product volatility), and $CHCl_3$ (20 mL) and aqueous NaOH (15 mL, 1.0 M) were added. After being stirred for 60−90 min, the biphasic solution was transferred to a separatory funnel, the $CHCl_3$ layer was removed, and the aqueous layer was further extracted with $CHCl_3$ (3 × 15 mL). The combined $CHCl_3$ extracts were filtered through a short bed of Celite (removes turbidity), and the Celite was subsequently washed with $CHCl_3$ (2 × 15 mL). The filtrate was then washed with saturated NH_4Cl (2 × 20 mL) [removes residual α-MBA] and then with brine (1 × 20 mL), dried over $MgSO_4$, filtered, and evaporated to dryness (rotary evaporate at ≤25 °C for short periods) to obtain the crude product (this material is used to determine the de). Purification by silica gel flash chromatography provides the mixture of diastereomers as a colorless viscous liquid (rotary evaporate at ≤25 °C for short periods); treatment with etheral HCl allows hydrochloride salt formation. Note that amine products **2** are considered to be semivolatile and converted to their HCl salts to enable high vacuum drying (defined as 0.5−2.0 mm Hg) to constant weight (generally for ≥12 h) for yield determination.

General Procedure: Catalytic $Yb(OAc)_3$, $Y(OAc)_3$, or $Ce(OAc)_3$ (Normal de). In a reaction vessel, the Lewis acid [$Yb(OAc)_3$ 10 mol %, $Y(OAc)_3$ (15 mol %) or $Ce(OAc)_3$ (15 mol %)][21] was added and subsequently evacuated under high vacuum for 5 min before flooding with nitrogen. To the vessel were added anhydrous methanol (2.5 mL, 1.0 M), ketone (2.5 mmol, 1.0 equiv), and (*S*)-α-methylbenzylamine (0.35 mL, 2.75 mmol, 1.1 equiv) and the mixture stirred for 20−30 min at the temperature at which the hydrogenation was performed (22 or 50 °C). A THF slurry of Raney-Ni (100 wt % based on the ketone, triturated with EtOH (×3) and then with anhydrous THF (×3) before addition) was transferred to the reaction mixture using 2.5 mL of anhydrous THF (final molarity of reaction solution is 0.5 M). The vessel was then pressurized to the indicated pressure 120−290 psi (8−20 bar) of hydrogen and stirred at room temperature or at 50 °C as indicated. At 12 h (<3 area % of ketone and intermediate ketimine by GC), the reaction mixture was worked-up as delineated in the above section (General Procedure: Stoichiometric $Yb(OAc)_3$ (Enhanced de)).

General Procedure: Brønsted Acids (Normal de). The reaction vessel was evacuated under high vacuum for 5 min before flooding with nitrogen. To the vessel were added anhydrous methanol (2.5 mL, 1.0 M), acetic acid (20 mol %), ketone (2.5 mmol, 1.0 equiv) (**1**), and (*S*)-α-methylbenzylamine (0.35 mL, 2.75 mmol, 1.1 equiv), and the mixture was stirred for 20−30 min at the temperature at which the hydrogenation was performed (22 or 50 °C). The remaining procedural details should be followed as in the above section (General Procedure: Catalytic $Yb(OAc)_3$, $Y(OAc)_3$, or $Ce(OAc)_3$ (Normal de)).

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Supporting Information Available: Detailed experimental procedures are provided for each amine (**2**) synthesized, and all compounds have been previously and fully characterized.[1c] ^1H and ^{13}C NMR data for amines showing enhanced de (**2a**−**f**) is provided; GC chromatograms are provided for all amines **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(44) The mechanism presented here (Scheme 3) is more likely than those in which simple ligation of $Yb(OAc)_3$ to the in situ formed *cis*- and *trans*-ketimine mixture allows improved facial selectivity for the addition of hydrogen. This is supported by the fact that no other lanthanide or transition metal acetate, chloride, or triflate (over 30 individual metals were examined) was identified as capable of providing enhanced de; and importantly other ytterbium salts, e.g., $YbCl_3$ and $Yb(OTf)_3$, did not allow enhanced diastereoselectivity (Table 1). Furthermore, the rate of reaction is unchanged in the presence $Yb(OAc)_3$, implying that the ligated ketimine is not the species being reduced but instead the free ketimine. Finally, scenarios in which only one of the ketimine diastereomers is ligated to $Yb(OAc)_3$ are unlikely because catalytic quantities of $Yb(OAc)_3$ do not allow enhanced diastereoselectivity.

(45) $Yb(OTf)_3$ could in theory undergo a similar ketimine isomerization process via its sulfonate oxygen but as noted previously only provided the alcohol byproduct under the reductive amination conditions noted here (Table 1), implying it is too Lewis acidic. Regardless, when we synthesized and then treated the *N*-α-MBA ketimine of 2-octanone with $Yb(OTf)_3$ (110 mol %) the desired product **2d** was noted, albeit without enhanced stereoselectivity.

(46) For references regarding imine formation in general, see ref 1c, p 1291.