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Asymmetric Reductive Amination: Convenient Access to Enantioenriched Alkyl-Alkyl or Aryl-Alkyl Substituted α-Chiral Primary Amines

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Abstract: A two-step procedure for producing optically active, high value primary amines has been developed. The first and key step is the asymmetric reductive amination of a prochiral alkyl alkyl (acyclic or cyclic) or aryl alkyl (acyclic or cyclic) ketone with (*R*)- or (*S*)-α-methylbenzylamine (α-MBA). The normally stepwise excessive procedures of chiral auxiliary approaches are avoided by simultaneously incorporating the auxiliary and a new stereogenic center at the former carbonyl carbon of the ketone during step one. Specifically, step one is the hydrogenation (4–8 bar) of a prochiral ketone substrate in the presence of α-MBA, a Lewis acid [$Ti(O\text{-}i\text{-}Pr)_4$, $B(O\text{-}i\text{-}Pr)_3$, $Al(O\text{-}i\text{-}Pr)_3$, or $Zr(O\text{-}i\text{-}Pr)_4$], and a heterogeneous hydrogenation catalyst (Raney-Ni, Pt-C, Pd-C, Ru-C, or Rh-C), providing the amine diastereomers **2** in good to excellent yield and diastereoselectivity. Depending on the ketone examined (acyclic *vs.* cyclic, alkyl alkyl *vs.* aryl alkyl, sterically encumbered *vs.* unencumbered), the correct combination of heterogeneous hydrogenation catalyst, solvent, and temperature is crucial for allowing high yield and *de* with practical reaction times (generally 6–20 h). Performing the reaction in the absence of one of the indicated Lewis acids results in the formation of large amounts of alcohol by-product (>25%). Step two, hydrogenolysis, allows smooth removal of the chiral auxiliary providing α-chiral primary amines in good overall yield (5 examples 71–78%, 1 example 64%) and in 66–98% enantiomeric excess. This two-step strategy is noteworthy because: 1) it is yield and stepwise efficient; 2) all the reagents are inexpensive and already used by the pharmaceutical industry; 3) a broad range of ketone substrates are suitable; 4) either enantiomeric form of the α-chiral amine product can be produced; 5) the reaction conditions are mild; and 6) the process is amenable to scale-up.

Keywords: aliphatic amines; asymmetric reductive amination; chiral amines; enantioenriched amines; heterogeneous hydrogenation catalysts; Lewis acids; titanium alkoxides

Introduction

In the last decade, the synthesis of chiral pharmaceutical drugs has steadily increased and now represents one-third of all drug sales worldwide.[1] Furthermore, it is estimated that 80% of all drug candidates presently being developed are chiral.[2] This increased demand for enantiopurity has elevated α-chiral amine[3] synthesis into a new era of importance such that it is now considered a high technology growth area by industry.[4] Examples of α-chiral amine-containing pharmaceutical drug targets are Elanapril, Sibutramine, Rivastigmine, and the billion-dollar drugs Flomax and Lisinopril (Figure 1). The key step in the synthesis of these pharmaceutical drugs, many alkaloid natural products, and some agrochemicals[4c] is the generation of an α-chiral amine. Less structurally complex α-chiral amines frequently find use as chiral ligands, chiral auxiliaries, or resolving agents.

Recent and significant advancements have been made concerning diastereoselective and enantioselective: hydrogenation of enamides,[5,6] 1,4-addition of amines to enones,[7] chemical[8a] and enzymatic[8b,c] reductive amination of α-keto acids, and remote amination *via* C–H insertion.[9] These methods rely on pendant substrate functionality to induce high stereo-

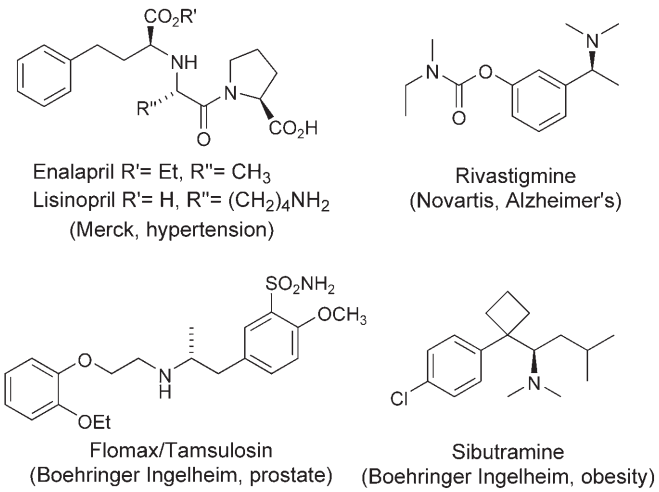


Figure 1. Pharmaceutical drugs containing α-chiral amine stereocenters.

selectivity, the focus here is on the synthesis of unfunctionalized α-chiral primary amines. Comprehensive reviews of α-chiral amine synthesis are available.[1,2,4e,10]

A different set of strategies is required for the synthesis of unfunctionalized α-chiral amines and can be generalized as: 1) diastereoselective carbanion addition to chiral aldimine or ketimine derivatives;[11,12] 2) enantioselective sequential amination-alkylation of aldehydes (carbanion addition to *in situ* formed aldimine derivatives);[8c,13,14] 3) enantioselective hydrogenation[15] or hydrosilylation[16] of *N*-alkyl- or *N*-arylimines; 4) enantioselective hydrogenation[10e,17] or transfer hydrogenation[4d,18] of *N*-phosphinylimines, preferably over other *N*-functionalized imines, e.g. −OR,−SO_2R, or−NR_2; 5) asymmetric reductive amination of ketones using hydrides,[19] hydrogen,[20] or transfer hydrogenation[21] conditions; and 6) those methods employing organocatalysis.[22] In particular these methods are capable of synthesizing α-alkyl-aryl-substituted chiral amines, but few of them are capable of efficiently synthesizing α-alkyl-alkyl-substituted chiral primary amines in good overall yield and *ee* (Figure 2).

When the above body of research is examined as a whole no strong trends can be definitively stated, but those methods using hydrides, molecular hydrogen, or transfer hydrogenation conditions generally excel at differentiating dissimilar α,α-substitution patterns for amine products arrived at from ketones [R_LC(O)R_S], while alkylmetal additions are superior at differentiating similar sized substituents originating from aldehydes [$R_{M'}$C(O)H] and the source of carbanion (R_M) (Figure 2). At the present stage of the developmental cycle, it can be stated that the two main strategies ('hydrogen addition' *vs.* carbanion addition) complement one another.

Results and Discussion

The diastereoselective reduction of chiral ketimines has been previously reported on, but has not been fully explored using the common chiral ammonia equivalents (*R*)- and (*S*)-α-methylbenzylamine (α-MBA), (*R*)- and (*S*)-phenylglycinol, (*R*)- and (*S*)-phenylglycine amide (PGA), and (*S*)- or (*R*)-*tert*-butanesulfinamide. Because α-MBA is by far the least expensive, and available in both enantiomeric forms in kg quantities, it has been more extensively examined. Despite this, only a handful of comprehensive studies have focused on the reduction of alkyl-alkyl and/or aryl-alkyl-*N*-α-methylbenzylketimines,[23–25] while many reports can be found describing the results from

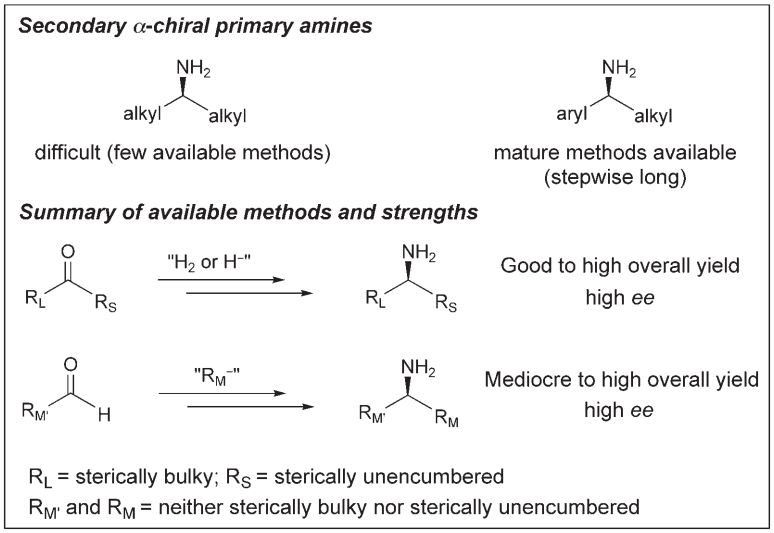


Figure 2. General overview of unfunctionalized α-chiral amine synthesis.

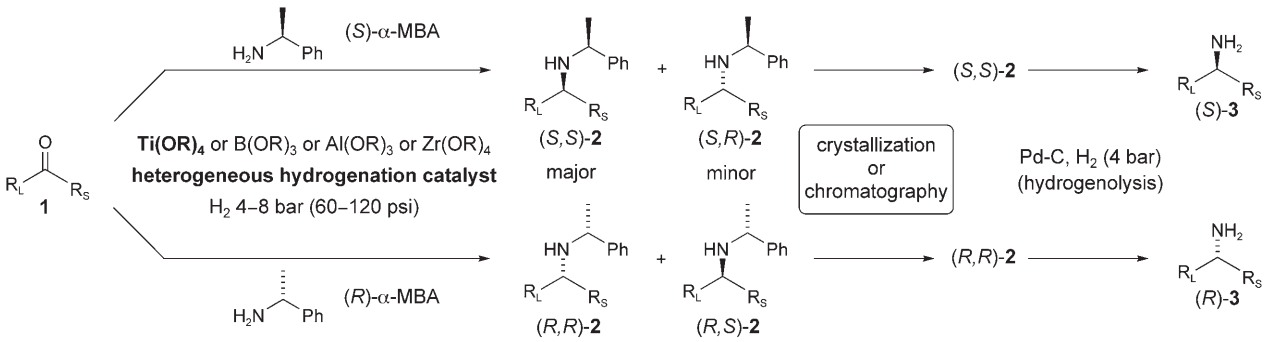
studying a single ketimine (generally for the advancement of a drug candidate).[26,27]

After reviewing the above literature we came to the conclusion that imine formation is not as straightforward or high-yielding as generally assumed. The standard dehydration conditions (refluxing toluene, Dean–Stark trap), with[28] or without[15a] catalytic *p*-TsOH,[29] can require long reaction times (36–120 h) and may not provide a high yield of the imine. Refluxing conditions can be avoided but only when excessively large wt-equivs. of molecular sieves are employed.[16c,30] Additionally, these protocols often call for the distillation of the imine product before their use.[15a,16c,23c,30] When the above-mentioned methods fail, or provide low yield of the imine, the procedure is generally to combine equal molar quantities of the ketone and amine, cool to −35 °C or 0 °C, and then add Et_3N and $TiCl_4$ to obtain the ketimine.[16d,23c,27,31] Other researchers have noted related problems for aldimine formation[32] although in our experience this is much less problematic.

Noting the above limitations of imine formation, we pursued a two-step strategy for the synthesis of primary amines, that avoided the isolation of imines (Scheme 1). The first step, asymmetric reductive amination of prochiral ketones **1** with (*R*)- or (*S*)-α-MBA, provides diastereomerically enriched secondary amines **2** (Scheme 1); the second step, hydrogenolysis of the chiral auxiliary, reliably affords high yields (85–95%) of the enantioenriched primary amines **3**. Particularly noteworthy of our method is the ability of aliphatic prochiral ketones to serve as good to excellent substrates. The use of aliphatic ketones for α-alkyl-alkyl-substituted chiral amine synthesis has been, and continues to be, a major stumbling block (Figure 2).

In principle, reductive amination is the most synthetically direct and efficient method for amine synthesis,[33,34] and our development of an asymmetric Lewis acid variant, using α-MBA, has been crucial for obtaining the high overall yields and *ee*s reported here. Aiding such examinations is the commercial availability of a large number of structurally diverse ketones which, unlike their aldehyde counterparts, are not prone to oxidation on storage. In our initial report, which demonstrated the first use of Ti(O-*i*-Pr)$_4$ and Raney-Ni for asymmetric reductive amination, the principal correlation examined was the change in diastereoselectivity upon changing the aliphatic group size on 2-alkanones.[20f,35] We now elaborate further on these substrates, but more importantly show that the method is applicable to more structurally and electronically diverse prochiral ketones. Our new findings show that optimal diastereoselectivity, yield, and reaction rate, very much depend on the heterogeneous hydrogenation catalyst employed, with solvent, temperature, and molarity playing critical fine tuning roles in the order stated.

In continuation of our initial 2-alkanone substrates studies, we have now examined 2-butanone, 2-hexanone, pinacolone, and acetophenone. Inclusion of these substrates, with those studied earlier, now allows a complete spectrum of basic 2-alkanones to be evaluated from the perspective of yield and *de* (Table 1). The greater the steric bulk of the substituent, R, on the 2-alkanone, $RC(O)CH_3$, the greater is the enhancement in diastereoselectivity to a point. For example, proceeding from R = ethyl, to *iso*-butyl, and then to *iso*-propyl, dramatically increases the *de* from 74 to 93 to 98% (Table 1, entries 6, 4, 2, respectively); but even at a reaction temperature of 50 °C pinacolone (a *tert*-butyl ketone discussed shortly) provided little of the desired product. Comparison of the straight-chain 2-alkanones: 2-butanone (**1f**), 2-hexanone (**1h**), and 2-octanone (**1g**) (Table 1, entries 6–8), showed 2-hexanone (**1h**) with appreciably lower *de* than the other two straight-chain 2-alkanones. These results were consistent over multiple examinations and all attempts to find coexisting impurities, which might be amplifying the *de* of the 2-butanone or 2-octanone products **2f** or **2g**, or decreasing the *de* of the 2-hexanone product **2h**, failed. Because there is no obvious reason for this non-linear progression of *de*, we decided to further validate our 2-butanone result. Hydrogenolysis of the reductive amination product **2f** (74% *de*, achiral GC column) confirmed the *ee* of the



Scheme 1. Asymmetric reductive amination: facile access to α-chiral primary amines.

Table 1. 2-Alkanones [$RC(O)CH_3$] requiring the heterogeneous hydrogenation catalyst Raney-Ni.[a]

Entry	Ketone	R	Solvent	Time [h]	Product	Yield [%]	*de* [%]
1	**1a**	*c*-hexyl	MTBE	11	**2a**	90	98
2	**1b**	*i*-propyl	hexane	10	**2b**	78	98
3[b]	**1c**	phenyl	EtOAc	8	**2c**	85	95
4	**1d**	*i*-butyl	hexane	9	**2d**	79	93
5	**1e**	$PhCH_2CH_2$-	DCM	11	**2e**	89	80
6[b]	**1f**	ethyl	THF	10	**2f**	94	74
7	**1g**	*n*-hexyl	THF	17	**2g**	90	72
8[b]	**1h**	*n*-butyl	DCM	8	**2h**	79	66

[a] Ketone (1.0 equiv.), (*S*)- or (*R*)-α-MBA (1.1 equivs.), $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 equivs.), solvent (0.5–0.8 M), H_2 (4.1 or 8.3 bar [60 or 120 psi]), Raney-Ni.
[b] New Raney-Ni results, see ref.[20f] for the previously published ketone entries: 1,2,4,5,7.

Table 2. Effect of heterogeneous hydrogenation catalyst on the diastereoselectivity of diverse ketone substrates.[a]

Entry	Starting ketone	Solvent	Product	Raney-Ni	Pt-C	Pd-C	Rh-C	Ru-C
1	1-phenylbutanone (**1j**)	EtOAc	**2j**	*94*	31	68	58[b]	-[c]
2	2-butanone (**1f**)[d]	THF	**2f**	*74*	41	43	36	40
3	pinacolone (**1k**)[e]	hexane	**2k**	-[b,f]	*87*	-[b,f]	-[b,f]	-[c]
4	benzosuberone (**1n**)[d]	EtOAc	**2n**	-[b]	50[b]	*76*	50	0

[a] Indicated *de*s represent the first aliquot showing no ketone before 24 h, or the *de* at 24 h, and were determined using GC area %.
[b] < 25 % of the diastereomeric products were formed at 24 h.
[c] 100 % starting ketone.
[d] The temperature for all 2-butanone reactions was 30 °C.
[e] The temperature for all reactions was 50 °C.
[f] Unable to determine the *de* due to overlap by the dominant species, i.e., the corresponding imine.

2-aminobutane product (**3f**) at 74 % (chiral GC column).

Encouraged by our results with 2-alkanones and Raney-Ni, we next examined a variety of prochiral ketone substrate classes for greater structural and electronic diversity.[36] They can be categorized as follow: acyclic aryl alkyl ketones, cyclic alkyl alkyl ketones, and cyclic aryl alkyl (benzocyclic) ketones. Within these categories, we also examined sterically encumbered substrates. All of these categories of ketones act as good to excellent substrates for our asymmetric reductive amination methodology, but only when the appropriate heterogeneous hydrogenation catalyst is used.

To define and optimize substrate class-specific conditions, heterogeneous hydrogenation catalyst screening proved to be the most critical starting point (Table 2). Further fine tuning, of *de* and yield, could then be realized by optimizing the solvent (Table 3), temperature, equivalents of α-MBA, and $Ti(O\text{-}i\text{-}Pr)_4$, and the molarity. An overview of the heterogeneous hydrogenation catalysts studied with the corresponding influence on diastereoselectivity can be garnered from Table 2. From this reference point, and further ketone substrate data, specific classes of substrates emerged as requiring specific heterogeneous hydrogenation catalysts for optimal stereoselectivity during reductive amination (Figure 3 and Figure 4). They can be loosely classified as follows: 1) Raney-Ni substrates are acyclic alkyl alkyl [e.g., 2-alkanones (**1a**–**1h**) and *iso*-propyl *n*-propyl ketone **1i**] or acyclic aryl

Table 3. Example of solvent screening: 2-octanone (**1g**).[a]

Entry	Solvent	*de* [%] of **2g**[b]	Ketone remaining [%][b]
1	THF[c]	72	0
2	CH_3OH	70	5
3	hexane	67	2
4	dichloromethane	66	1
5	toluene	66	4
6	MTBE[c]	65	0
7	1,2-dimethoxy-ethane[c]	62	0
8	DMF	54	8
9	DMSO	49	11

[a] 2-Octanone (2.5 mmol), (*R*)-α-MBA (1.15 equivs.), $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 equivs.), Raney Ni (100 wt %), H_2 (8.3 bar/120 psi), 22 °C. Data were collected at 24 h.
[b] GC area %.
[c] No ketone remained after 6 h.

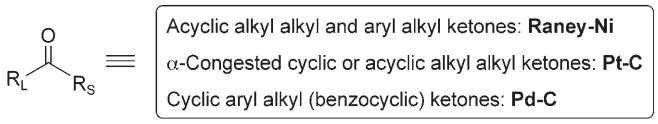


Figure 3. Class of ketone substrate *vs.* optimal heterogeneous H_2 catalyst.

alkyl [e.g., 1-phenylbutanone (**1j**)] ketones that lack an α-tertiary group, e.g., *tert*-butyl moiety, directly attached to the carbonyl carbon; 2) Pt-C substrates are acyclic [e.g., pinacolone (**1k**)] or cyclic alkyl alkyl ketones [e.g., 2,2-dimethylcyclopentanone (**1l**)] that contain a high degree of α-carbonyl steric congestion, i.e., have a tertiary carbon directly attached to the carbonyl carbon; and 3) Pd-C substrates are cyclic aryl alkyl ketones, e.g., the benzocyclic ketones α-tetralone (**1m**) and benzosuberone (**1n**). General experimental protocols have been established for these different classes of ketones, and readily allow semi-optimized conditions to be established for yet untested but similarly functionalized prochiral ketones. Aryl aryl ketones have yet to be examined.

The general reaction conditions are as follows. To the ketone [in an anhydrous solvent (0.5–0.8 M)] is added (*R*)- or (*S*)-α-MBA (1.05 or 1.1 equivs.) and Ti(O-*i*-Pr)$_4$ (1.0–1.25 equivs.). The heterogeneous hydrogenation catalyst is then added and the reaction is hydrogenated at 8.3 bar (120 psi). For approximately half of the ketones examined, stirring the reaction for 90 min before addition of the heterogeneous hydrogenation catalyst allowed slightly faster overall reaction times and slightly higher *de*s. Hydrogen pressures of 4.1 bar (60 psi) can be used, but the reaction times lengthen considerably. Monitoring of reaction progression and diastereoselectivity is straightforward and can be simultaneously obtained from one GC run without derivatization of the sample (see Supporting Information). All quoted yields are isolated yield data after chromatography.

For our screening reactions 70–100 wt% Raney-Ni was commonly used, but we have demonstrated that 20–40 wt% is generally sufficient on the gram scale (see table in Supporting Information). For example, when 5.0 g (69.3 mmol) of 2-butanone (**1f**) were reductively aminated with 30 wt% of Raney-Ni,[37] no starting material remained after 12 h and an isolated yield of 94% with 74% *de* was observed and is consistent with the our small scale (2.5 mmol) screening reaction. Pt-C and Pd-C are used at 0.30 mol% and 0.23 mol% catalyst loadings, respectively. All of the heterogeneous hydrogenation catalysts used are commercially available and we found consistent yield and *de* when different batches of the same catalyst type (Ni, Pt, or Pd) were examined from the same supplier. A future study will be required to investigate the effect of different heterogeneous metal catalyst preparations and alternative supports. Figure 4 provides representative examples from each ketone substrate category examined, they are grouped according to the optimal heterogeneous hydrogenation catalyst.

Pt-C and Pd-C have been previously examined for titanium(IV) reductive amination, but not in a substrate or comparative hydrogenation catalyst manner. The previous lone example with Pt-C fits nicely into the category defined above for α-sterically congested

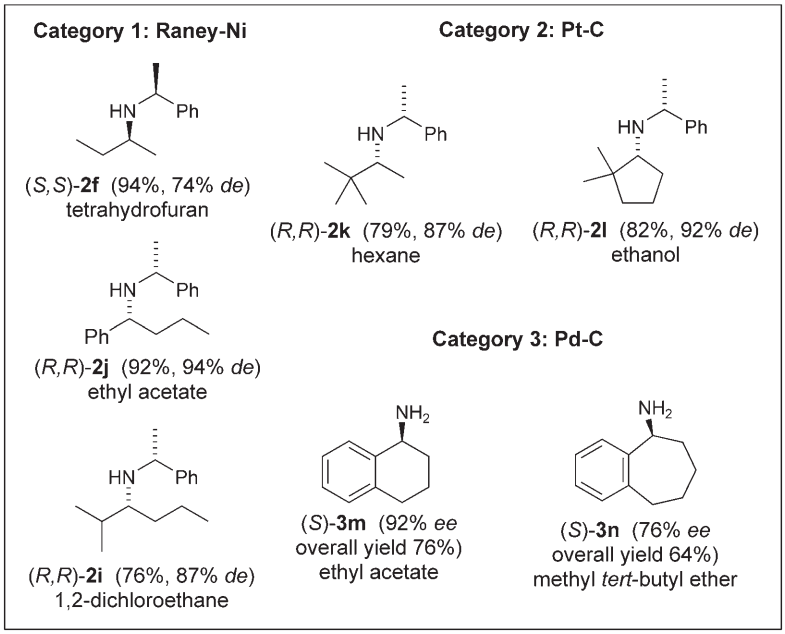


Figure 4. Correlation of structure, heterogeneous H_2 catalyst, and diastereoselectivity.

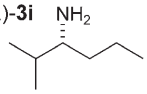
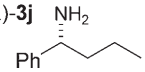
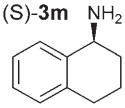
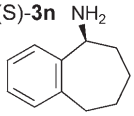
ketones (Figure 4, category 2).[20g] A previous asymmetric reductive amination study[20d] of aryl alkyl ketones and α-MBA using Pd-C and Ti(O-*i*-Pr)$_4$ provided significantly lower *de* based on direct comparison with our Raney Ni acetophenone (**1c**) result (Table 1, entry 3); and by analogy with our examination of 1-phenylbutanone (also a Raney-Ni substrate, Figure 4, structure **2j**). These combined findings reaffirm that acyclic aryl alkyl ketones are indeed reductively aminated in superior diastereoselectivity with Raney-Ni and not with Pd-C.

The use of increased mole percents of either Pt or Pd provided increased reaction rates, but in general resulted in significantly lower *de*s, among other complications. For example, when benzosuberone (**1n**), which provides the reductive amination product in 76% *de* at 0.23 mol% Pd-C loading, but with the long reaction time of 36 h, was treated with 2.5 mol% of Pd-C, the de dropped precipitously, declining to 55%. Another example is pinacolone (**1k**) (a Pt-C substrate), when treated with 0.15 mol% of Pd-C only 17% of the desired product was obtained at 50 °C after 24 h. When the amount of Pd-C was increased to 0.75 mol% or 2.5 mol%, the area% of the desired product increased but large amounts of the ketone remained, even at elevated temperatures. Furthermore, at these high catalyst loadings complications arose from competitive alcohol formation and partial hydrogenolysis of the desired product.

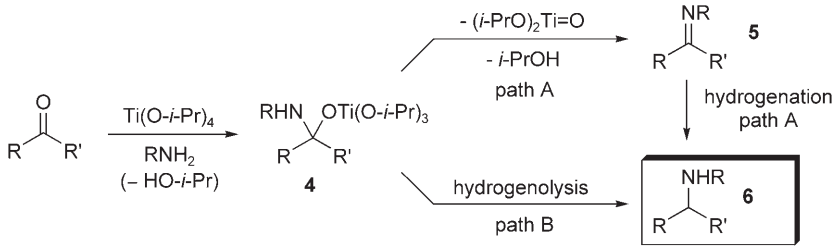
Isolation of the corresponding primary amines **3** was straightforward and proceeded in high yield after hydrogenolysis of the chiral auxiliary, a procedure routinely practiced in the pharmaceutical industry.[1,5b,27] To our surprise, the hydrogenolysis step had to be optimized for each example, concerning the best source of Pd [Pd-C or Pd(OH)$_2$-C], and the need for an acid additive (AcOH) or lack thereof; but always allowed 85–95% yields to be achieved. Examples for three of the substrate categories (acyclic alkyl alkyl ketones, acyclic aryl alkyl ketones, and cyclic aryl alkyl ketones) are provided in Table 4. Perhaps the most interesting examples are those in which competitive regioselective hydrogenolysis can occur. This is the case when any aryl alkyl ketone is examined and we found regioselective cleavage of the desired benzylic C–N bond favorable, with the least hindered benzylic C–N bond being the most facile to cleave.

Because both steps of our method require hydrogen we were intrigued by the possibility of a one-pot sequential reductive amination-hydrogenolysis sequence leading directly to the primary amine **3** from ketones **1**. For the Pd-C specific ketones, α-tetralone (**1m**) and benzosuberone (**1n**) (Table 4, entries 4 and 5), this appeared to be a natural extension of our two-step procedure. In the end we found the highest yield and best overall reaction times could only be achieved when the crude reductive amination product was isolated, and CH_3OH and new Pd-C added to allow smooth hydrogenolysis. Thus in our hands an efficient

Table 4. α-Chiral primary amine synthesis: hydrogenolysis examples and overall yield.[a]

Entry	1° Amine **3**	Pd Source/Additive/Regioselectivity[b]	Overall yield [%][c]	*ee* [%][d]
1	(S)-**3f** 	Pd(OH)$_2$-C/AcOH/ > 99:1	71	74
2[e]	(R)-**3i** 	Pd-C/no additive/ > 99:1	71	87
3	(R)-**3j** 	Pd-C/no additive/8:1	74	90[f]
4	(S)-**3m** 	Pd-C/AcOH/ > 4:1	76	92
5	(S)-**3n** 	Pd-C/AcOH/ > 40:1	64	76

[a] All reactions performed in CH_3OH at 22 °C.
[b] Regioselectivity for step two (hydrogenolysis), desired/undesired benzylic cleavage ratio provided.
[c] Isolated yield data provided starting from the ketone.
[d] Determined by chiral GC (trifluoroacetyl derivative) or HPLC (benzoyl derivative) analysis of the of the primary amine.
[e] Previously reported, see ref.[20f] We have also converted benzylacetone (**1e**) to its corresponding primary amine (**3e**) in 78% overall yield (80% *ee*), see ref.[20f]
[f] The *de* for the starting material (**2j**) is 94%, see Figure 4.[39]



Scheme 2. Possible reaction pathways for Ti(O-*i*-Pr)$_4$ mediated reductive amination.

one-pot sequential reductive amination-hydrogenolysis procedure was not achieved.[38]

Concerning the use of Lewis acids, reductive amination is historically defined as the combination of a Brønsted acid, a ketone, an amine and a co-existing reductant.[40] The recent evolution of titanium(IV) alkoxides, as mild Lewis acid replacements for Brønsted acids, owes its genesis to a clever modification of titanium amide chemistry[41] demonstrated by Mattson et. al in 1990.[42] By prestirring a ketone, an amine, and Ti(O-*i*-Pr)$_4$ (neat), followed by the addition of EtOH and $NaBH_3CN$, the desired reductive amination product was formed (Scheme 2). This marked the beginning of efficient Lewis acid-based racemic reductive amination.

By now the use of Ti(O-*i*Pr)$_4$ is extensively documented for the formation of chiral sulfinyl aldimines and ketimines,[11,43] racemic reductive amination in combination with hydride reagents,[44] and, more recently, for asymmetric reductive amination with hydride reagents[19] or hydrogen.[20d,f,g] Note that while $TiCl_4$ or Ti(O-*i*-Pr)$_4$ can be used for ketimine formation (after aqueous work-up), $TiCl_4$ is not an effective Lewis acid for our reductive amination methodology. Additionally, we have now found that Ti(OR)$_4$ can be replaced with equivalent stoichiometric quantities of the Lewis acids B(O-*i*-Pr)$_3$, Al(O-*i*-Pr)$_3$, or Zr(O-*i*-Pr)$_4$, while maintaining the same *de* for the secondary amine product **2** (Scheme 1). These new Lewis acids provide added flexibility for future research,[45] but generally require longer reaction times than Ti(O-*i*-Pr)$_4$. These slower reaction rates can be overcome by using higher hydrogenation pressures and/or increased reaction temperatures, usually without detrimental effects on the *de* of the product. It should be noted that previous research has been published indicating the usefulness of aluminum alkoxides.[19c,20g] Regarding the use of catalytic quantities of Ti(O-*i*-Pr)$_4$, the use of 50 mol% generally doubled or tripled reaction times and small amounts of the ketone still remained, but the *de* remained constant.

The origin of diastereoselective control in *N*-α-methylbenzylketimine reduction, in relation to heterogeneous hydrogenation catalysts, has been previously reported,[1,10d,20a,b,29] but the definitive mechanism at the heterogeneous metal surface is still not rigorously understood. The affinity of the aromatic ring, of α-MBA, for the metal catalyst surface has been implicated as a key element of stereocontrol when examining this auxiliary for reductive amination studies.[20a]

It has been suggested that Ti(O-*i*-Pr)$_4$-based reductive aminations proceed through hemiaminal titanate intermediates (**4**) (Scheme 2), based on IR spectroscopy before addition of the reductant.[42] The question of whether the hemiaminal titanate (**4**) is directly hydrogenolyzed to the amine product **6** (path B), or whether it first collapses to an imine **5** (path A), which to date has eluded spectroscopic verification, and is then reduced, has yet to be clarified. As with many past studies of reductive amination, defining whether one or several constructive mechanistic pathways are operative is not trivial.[33,34] It is expected that the design of one or more eloquent experiments could help prove if one mechanistic pathway prevails or not. Additionally kinetic studies taking advantage of ^{13}C and/or ^{49}Ti NMR measurements (our basic investigations using ^1H NMR were inconclusive) could lead to beneficial mechanistic insight, but were beyond the scope of the present study.

With this reference point, we did probe for further insight into the basic mechanism by examining the effect of several reductants on the fate of the hemiaminal titanate formed by thoroughly examining the reductive amination of benzylacetone (**1e**) with α-MBA (Table 5). The most striking finding against the hydrogenolysis possibility (Scheme 2, path B) is that BH_3, well documented as an imine reducing agent, allows fast reduction of the hemiaminal titanate at 2 °C (Table 5, entry 4). 9-BBN, even at the elevated temperatures of refluxing THF, did not allow product formation (**2e**), presumably due to steric congestion. Additionally, common hydride reagents (Table 5, entries 1–3) allowed facile product formation, and these results again favor mechanistic pathway A (Scheme 2). The hydrogenolysis pathway cannot be ruled out because it is possible that some reaction conditions may favor collapse of the hemiaminal titanate to an imine (e.g., under the basic conditions of a hydride reagent) while other reaction conditions may not. With the last possibility less likely, a rudimentary assumption can be made that *in situ* imine formation is occurring.

Table 5. Comparative systems for asymmetric reductive amination of $PhCH_2CH_2C(O)CH_3$ (**1e**) with (*R*)- or (*S*)-α-MBA.

Entry	General reaction conditions[a]	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*de* [%]
1	AcOH/$NaB(OAc)_3H$ (1.5 equivs.)	THF	2	18	96	21
2	$Ti(O\text{-}i\text{-}Pr)_4$/$NaB(OAc)_3H$ (1.5 equivs.)	THF	2	14	71	18
3	$Ti(O\text{-}i\text{-}Pr)_4$/$NaBH_4$ (1.5 equivs.)	EtOH	2	12	83	47
4	$Ti(O\text{-}i\text{-}Pr)_4$/$BH_3$ (1.5 equivs.)	THF	2	3	98[c]	55
5	$Ti(O\text{-}i\text{-}Pr)_4$/9-BBN (1.5 equivs.)	THF	2	16	sm[d]	-
6	$Ti(O\text{-}i\text{-}Pr)_4$/9-BBN (1.5 equivs.)	THF	22	16	sm[d]	-
7	$Ti(O\text{-}i\text{-}Pr)_4$/9-BBN (1.5 equivs.)	THF	65	16	sm[d]	-
8	**$Ti(O\text{-}i\text{-}Pr)_4$/70 wt % Raney-Ni**	**CH_2Cl_2**	**22**	**11**	**89, 98[c]**	**80**
9	$Ti(O\text{-}i\text{-}Pr)_4$/100 wt % Raney-Ni	EtOH	22	10	96[c]	78
10	$Ti(O\text{-}i\text{-}Pr)_4$/100 wt % Raney-Ni	THF	22	10	97[c]	79
11	AcOH[e]/70 wt % Raney-Ni	THF	50	48	82[c]	78
12	AcOH[f]/70 wt % Raney-Ni	AcOH	22	24	61[c]	74
13	*p*-TsOH[e]/70 wt % Raney-Ni	EtOH	22	12	43 [g]	-[i]
14	*p*-TsOH[h]/70 wt % Raney-Ni	EtOH	22	12	83 [g]	78
15	*p*-TsOH[h]/70 wt % Raney-Ni	THF	22	22	14[c]	-[i]
16	*p*-TsOH[h]/70 wt % Raney-Ni	CH_2Cl_2	22	22	2[c]	-[i]
17	No additive/70 wt % Raney-Ni	EtOH	22	10	55 [g]	78

[a] The solvent (0.5 M), benzylacetone (**1e**) (2.5 mmol), (*R*)- or (*S*)-α-MBA (1.1 equivs.), and $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 equivs.) were prestirred for 1 h and then the reductant was added. For entries 1–7 after 3 h of prestirring without solvent, the solvent (0.5 M) and reductant were added. Entries 11–17 were not prestirred.
[b] Isolated yield after chromatography, unless otherwise stated.
[c] GC area %, remaining area % is the starting ketone.
[d] Starting material.
[e] 100 mol %.
[f] AcOH was used as the solvent (0.50 M).
[g] GC area %, remaining area % is the alcohol from ketone reduction.
[h] 5 mol %.
[i] Unable to determine *de* due to low product formation.

Finally, we have examined further variations of our present method and the classically reported Brønsted acid methods, and have found all of them to be inferior (conversion, yield and *de*) to our Lewis acid-mediated method reported here (Table 5). These results clearly establish the value of the present method for asymmetric reductive amination. Furthermore the Lewis acid methods tolerate the presence of Brønsted acid-labile functional groups (e.g. acetonides, esters, silyl ethers, etc.) and others (carbamates, urethanes, tertiary amides, etc.)[44] on the substrates, and importantly Lewis acids are superior at suppressing alcohol by-product formation (ketone reduction) compared to Brønsted acid-mediated reductive amination (Table 5, compare entries 8 and 14).

Conclusions

At present the well established methods for α-chiral amine synthesis are not capable of synthesizing enantiopure *aliphatic α-chiral amines*, but the recent methods outlined in the introduction, and the methodology presented here are approaching this goal. These recently introduced methods are early in their developmental cycle and it can be expected that further research will lift one or more of them to the level of a truly general method that the non-expert can rely on for the synthesis of enantioenriched amines.

Our contribution, in pursuit of these goals, is the presently reported two-step procedure for producing enantioenriched primary amines from a diverse set of alkyl alkyl (cyclic or acyclic) or aryl alkyl (cyclic or acyclic) prochiral ketones. Key to these findings was the identification and development of Lewis acids for reductive amination in the presence of H_2, a heterogeneous hydrogenation catalyst, and the inexpensive chiral ammonia equivalent α-MBA. Our finding that several Lewis acids can replace $Ti(O\text{-}i\text{-}Pr)_4$ should provide added flexibility for future research regarding racemic, diastereoselective, and enantioselective reductive amination studies.

Finally, when compared to the multi-step procedures presently available, our results compare favorably with or exceed them with respect to yield, *ee*, ease of procedural set-up, and/or cost effectiveness. Furthermore, the process is amenable to scale-up. Additionally, keto ester (EtOAc has been successfully used as a solvent for the reductive aminations noted here) and dicarbonyl (e.g., aldehyde-ketone and diketone) substrates should be acceptable substrates. The last

category is noted because of the possibility for facile access to enantioenriched cyclic amines in one-pot.

Experimental Section

General Remarks

NMR spectra were recorded on a JEOL ECX 400 spectrometer, operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS (=0) or relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported in the scale relative to $CHCl_3$ (77.0 ppm) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad. The coupling constants are measured in Hertz. FT-IR spectra were obtained on Nicolet Avatar 370 spectrometer. Mass spectra were recorded on a Finnigan MAT 95 (EI) with an ionization potential of 70 eV. Elemental analyses were performed at Analytische Laboiratorien, Lindlar, Germany on an Elementar Vario EL III instrument. For amine products **2**, reaction progress and *dr* measurements were obtained using a Shimadzu GC-2010 instrument with a Rtx-5 amine column (Restec, 30 m × 0.25 mm); T_{inj} = 300 °C and T_{det} = 300 °C were always constant; Program A: 50 °C (1 min); then 20 °C min^{-1} to 280 °C, then hold 2 min; Program B: 50 °C (1 min), then 5 °C min^{-1} to 210 °C, then hold 2 min and Program C: 50 °C (1 min), then 14 °C min^{-1} to 280 °C, then hold 5 min. For hydrogenolyzed products (primary amines, **3**) the enantiomaric excess of the trifluoroacetamide derivative was determined by gas chromatography using a Shimadzu GC-2010 instrument on a Chiraldex B-DP column (Astec, 30 m × 0.25 mm); T_{inj} = 200 °C, T_{det} = 200 °C and carrier gas He at 23.6 psi were constant; Program D: 150 °C, isothermal, split ratio 100:1; Program E: 145 °C, isothermal, split ratio 100:1; Program F: 116 °C, isothermal, split ratio 100:1. The enantiomeric excess of the benzoyl derivative of **3f** was determined by HPLC using a Shimadzu CLASS-VP instrument on a Chiralcel OD-H column (Diacel, 0.46 cm × 25 cm); *n*-hexane/*i*-PrOH = 16/1, 0.1 mL min^{-1}, 254 nm, T_{col} = 15 °C, 22 bar. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 F_{254} and visualized under ultraviolet irradiation (254 nm). All reagents were obtained from Sigma–Aldrich and used without further purification. 99.999% grade Ti(O-*i*-Pr)$_4$ was used for all screening reactions (2.0–5.0 mmol) and 97.0% grade Ti(O-*i*-Pr)$_4$ was used for all large scale reactions (30–69 mmol). The (*R*)-α-methylbenzylamine was purchased from Aldrich (Catalog number, 115541, 98% pure and 95.5% *ee*) and (*S*)-α-methylbenzylamine was purchased from Aldrich (Catalog number, 115568, 98% pure and 97.5% *ee*). The Raney nickel (in water) was purchased from Fluka (Catalog number, 83440). Pd(OH)$_2$/C [≤ 50% water, 20 wt% loading (dry basis)] was purchased from Aldrich (Catalog number, 212911). Pd/C [≤ 50% water, 5 wt% loading (dry basis)] was purchased from Aldrich (Catalog number, 276707). Pt/C (1–4% water, 5 wt% loading) was purchased from Aldrich (Catalog number, 205931). All reactions were performed under an argon atmosphere and under anhydrous conditions.

General Procedure for Asymmetric Reductive Amination of Prochiral Ketones

In an anhydrous solvent (0.50–0.83 M) a prochiral ketone **1** (2.50–5.00 mmol), titanium tetraisopropoxide (1.25 equivs.), and (*R*)- or (*S*)-α-methylbenzylamine (1.00–1.10 equivs.) were combined and stirred at room temperature for 30 min. A heterogeneous catalyst, Raney Ni [70–100 wt%, pre-triturated with EtOH (×2) and then the anhydrous reaction solvent (×2)], Pt/C (0.30 mol%), or Pd/C (0.23 mol%), was then added and the vessel pressurized at 120 psi (8.3 bar) of hydrogen. At complete conversion (<1 area% of ketone by GC), the reaction mixture was quenched by stirring with aqueous 1.0 M NaOH (10–15 mL) for 1 h. The heterogeneous mixture was then filtered through a bed of celite and the celite subsequently washed with CH_2Cl_2 or EtOAc. The filtrate was concentrated (rotary evaporator, T ≤ 25 °C) to remove the low boiling organics and the remaining aqueous solution was then extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated (rotary evaporator, T ≤ 25 °C). The *de* values were then determined by analysis of the crude product.

The diastereomeric yield was determined after flash chromatography, using the following protocol. Due to the high volatility of most of the amine products **2**, the column fractions were rotary evaporated (T ≤ 25 °C), and then ethereal HCl (1.5–2.0 equivs.) was added. After very brief stirring, the ethereal solution of diastereomeric amine HCl salts was rotary evaporated and the resulting solid or viscous liquid high vacuum dried to constant weight (≥ 24 h). The major (*R,R*) or (*S,S*) diastereomer was isolated in pure form only after further careful flash chromatography of the diastereomeric mixture (free amine). All stereochemical assignments are based on previous literature examples and extension of those general trends.[20f]

Supporting Information

Characterization data for all products.

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[35] For previous investigations of asymmetric reductive amination using α-MBA and hydrogen, see refs.[19a,][20a,b,d]

[36] Note that an examination of 3-octanone failed to provide a reasonable *de* (<10%).

[37] This wt% corresponds to a turnover number of 46.2 (mmoles of ketone per gram of Raney-Ni) and is excellent concerning historically reported data pertaining to the use of Raney-Ni. See ref.[20f] for comparative data.

[38] Not examined were the following two possible solutions: 1) once the reductive amination reaction is complete, raise the hydrogen pressure to facilitate complete hydrogenolysis, or 2) for Raney-Ni or Pt-C ketones we never examined the possibility of completing the reductive amination reaction, and then simply adding Pd-C and continuing the hydrogenation to enable a one-pot (ketone to primary amine) reductive amination-hydrogenolysis sequence.

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[45] For example, for the use of chiral Lewis acid equivalents in combination with prochiral ketones and amines for enantioselective reductive amination, or as a starting point for the investigation of achiral Lewis acid derivatives thereof in the search for enhanced *de* and/or reaction rate with α-MBA or other amines.

