Step-Efficient Access to Chiral Primary Amines

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Abstract: Routes to enantioenriched amines are outlined that employ reductive amination and carbanion addition methods. The strategies require either one or two reaction steps from prochiral carbonyl compounds for the synthesis of the corresponding chiral primary amines.

Key words: chiral amine, enantiopure amines, reductive amination, cuprate addition, imine reduction

Introduction

Chiral primary amines are flexible building blocks that are often relied upon for the synthetic design of pharmaceutical drugs and alkaloid natural products by academic groups and process research chemists, while medicinal chemists need them for biologically relevant diversification of drug templates. Driven by these demands, the synthesis of chiral amines (non-amino acid) has undergone a broad transformation over the last twenty years.[1] A literature search of methods for the synthesis of chiral amines will identify many potentially suitable and diverse methods, but challenges remain, e.g. reaction step efficiency, functional group compatibility, and a lack of access to some chiral amine structural classes. From a larger perspective, a one-step method that will enable the stereogenic intermolecular insertion of nitrogen into advanced intermediates is desirable but not yet feasible.

Scope and Limitations

Figure 1 provides a summary of the amine structural classes that can be accessed using the methods summarized in this feature article. By 'access' we mean the chiral primary amine can be arrived at in very good overall yield, typically 60–80%, with good-to-high enantiomeric excess (80–99%) from a prochiral ketone or aldehyde.

The synthetic strategies and most often used reaction conditions for arriving at chiral primary amine products, such as those shown in Figure 1, are given in Scheme 1. Most of our research has focused on the reductive amination strategy, but when this strategy has failed to provide >80% ee, the carbanion strategy generally provided good-to-excellent yields and enantiomeric excesses; in short the methods complement one another. Importantly, both methods are step-economic: two reaction steps from a ketone or aldehyde to a chiral primary amine. It is of further note that we have recently developed a one-pot synthesis of chiral primary amines from ketones.

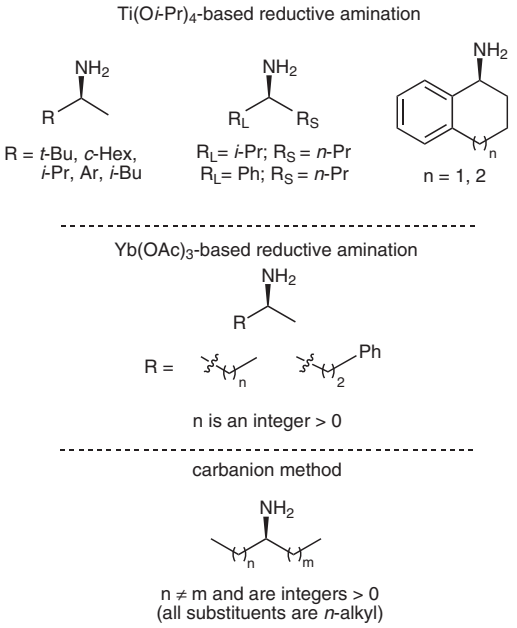

Figure 1 Accessible generic amine structural classes and some specific examples

The methods outlined here (Scheme 1) have a practical advantage: their technical simplicity, but both require a hydrogenolysis deprotection step. If low Pd/C loadings (0.5 mol%) are desired for the hydrogenolysis step, a pressure vessel capable of 15–20 bar (218–290 psi) H_2 and heating at 50–60 °C is required. If such an apparatus is not available, then inordinately high Pd/C loadings (5–10 mol%) with 4 bar (60 psi) H_2 at room temperature will often suffice.[2,3] A glovebox or specialized catalysts or syntheses thereof are not required, instead only commodity catalysts and reagents that are routinely used on an industrial scale are necessary.

The generic structures of Figure 1 do not address functional group compatibility, but the following co-existing moieties are possible: carbamates, urethanes, amides, acetonides, ethers, silyl ethers, and sterically hindered esters.[4] Further functional group compatibility needs to be explored, and limitations will certainly be encountered. For example, titanium(IV) isopropoxide based reductive amination methods will transesterify unhindered ester moieties, e.g. methyl or ethyl esters, into isopropyl es-

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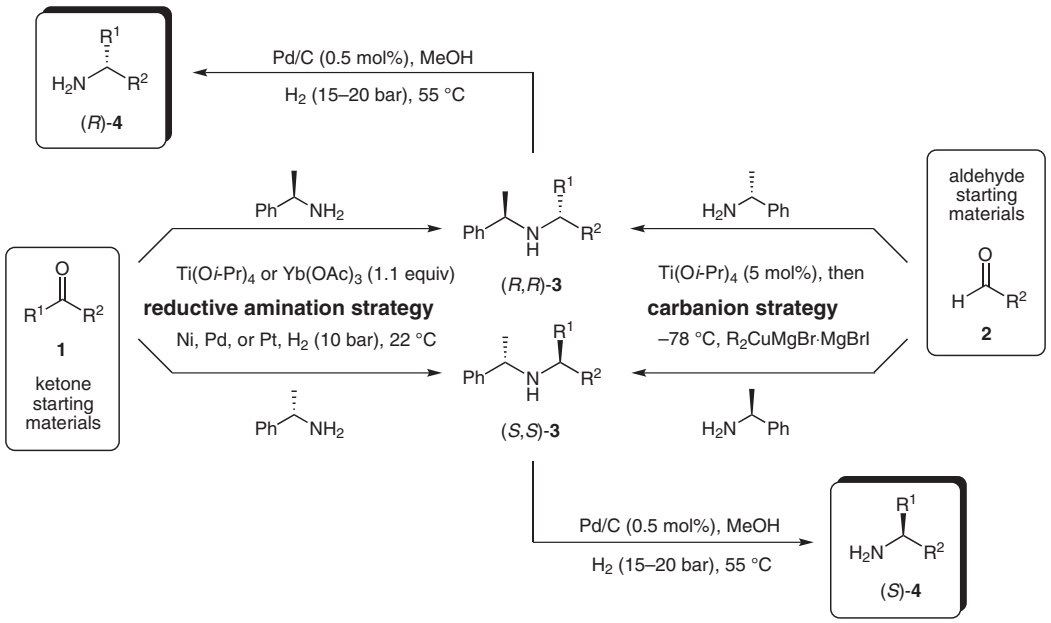


Scheme 1 Synthetic strategies for accessing chiral amines as illustrated in Figure 1

ters.[4d,5] Regarding non-compatible functionality, haloaromatics would be hydrogenolyzed under the reductive amination conditions,[6] and we were surprised to find that an aromatic fluoride underwent partial defluorination (6–10%).[7,8] Although not examined, the hydro-dehalogenation problem would potentially extend to alkyl halides, although alkyl fluorides, in our limited experience, are tolerated.[9] Finally, reaction conditions have been reported that ameliorate the hydro-dehalogenation problem and hold potential for incorporation into our reductive amination methodology.[10]

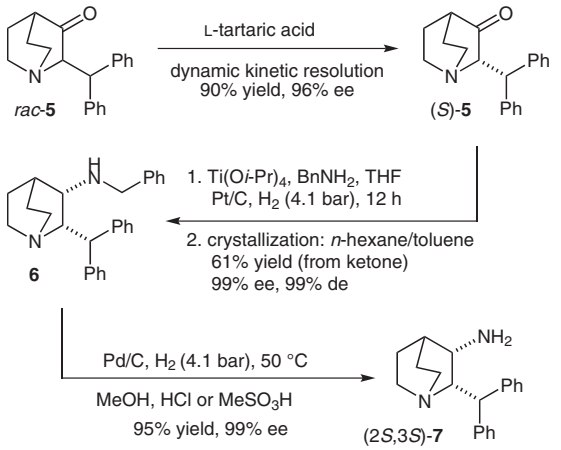
It is important to note that the reductive amination methods discussed here can be extended to the reaction of α-chiral ketones with achiral amines. This is noteworthy because it is the first demonstration, to the best of our knowledge, of reductive amination allowing the stereochemical integrity of an α-labile chiral ketone to be preserved. For example, ketone (*S*)-**5** (96% ee), an α-stereolabile chiral

Biographical Sketches

Thomas C. Nugent was born in 1967 in London (UK) but raised in California and Vermont (USA). He attended Virginia Polytechnic Institute and State University (Blacksburg, VA, USA) and completed his Ph.D. studies in natural product synthesis under the direction of Tomáš Hudlický in 1995. From 1996–1997 he held a postdoctoral position at the University of Liverpool (UK) investigating peptide-based epoxidation methodology with Stanley M. Roberts. He then entered the pharmaceutical industry as a process research chemist, working for DSM and Pfizer (San Francisco, CA, USA). In 2004 he became an assistant professor of chemistry at Jacobs University (Bremen, Germany).

Sofiya M. Marinova was born in 1992 in Veliko Tarnovo, Bulgaria. In the summer of 2011, she received her high school diploma from Aprilov National High School in Gabrovo, Bulgaria. Currently, she is a second year chemistry B.Sc. student at Jacobs University Bremen, Germany. Her research interests are in the area of asymmetric synthesis with a recent interest in organocatalysis, which she is pursuing within the laboratory of Professor Nugent.

ketone, was successfully reductively aminated to give diamine **6** without loss of the initial stereointegrity. Thus, we were able to demonstrate the most efficient synthesis of (2*S*,3*S*)-**7** to date, a pivotal substance P receptor antagonist building block (Scheme 2).[4a,11] Reductive amination of ketone (*S*)-**5** using the known Brønsted acid methods resulted in gross racemization.[4a] This general tactic, reaction of **5** to give **6** (Scheme 2), should be amenable to the reductive amination of other enantioenriched α-chiral ketones, e.g. hydroxy ketones, alkoxy ketones, etc., for more step-efficient chiral drug or natural product synthesis.

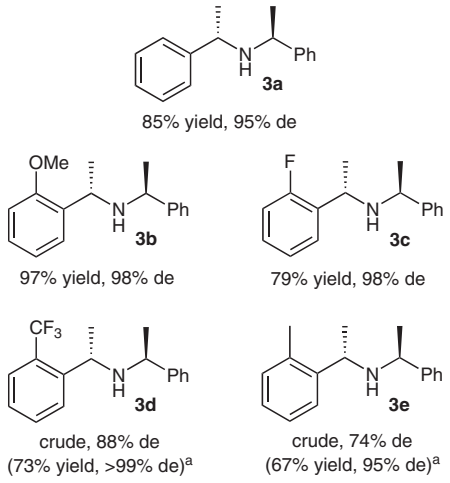


Scheme 2 Stereochemical preservation of an α-labile chiral ketone, (*S*)-**5**, during reductive amination: synthesis of a key quinuclidine intermediate **7**

The forward-going discussion examines the use of achiral carbonyl compounds for chiral primary amine synthesis (Scheme 1). Both strategies (reductive amination and carbanion addition) proceed through secondary amines **3**. When mediocre diastereoselectivity is noted, salt formation, e.g. with phthalic acid or hydrogen chloride, followed by crystallization allows high diastereomeric enrichment of amines **3** with good-to-excellent yields.[12] It is important to note that the diastereomeric excess of the secondary amines **3** and the corresponding enantiomeric excess of the primary amines **4** are consistent for all methods examined.[13,14]

Stoichiometric Titanium-Based Reductive Amination

The yields and diastereoselectivities for chiral amine structures **3a**–**e** arrived at using the titanium(IV) isopropoxide based reductive amination methods with prochiral methyl aryl ketones are shown in Figure 2. Acetophenone (**1a**) is not a practical substrate to study if the goal is the corresponding primary amine, nonetheless it offers direct insight into the stereoelectronic effects of an aromatic substituent on the carbonyl carbon, and the starting point for understanding aryl methyl ketone substrate diastereoselectivity. Acetophenone (**1a**) underwent titanium(IV) isopropoxide based reductive amination to give bis[(*R*)-1-phenylethyl]amine (**3a**) in very good yield and high diastereomeric excess (Figure 2), and it is predicted that similar product profiles would be noted when examining *para*- or *meta*-substituted acetophenones. The reductive amination of *ortho*-substituted acetophenones with diverse electronic character (F, CF_3, Me, OMe) was pursued, and successfully led to the formation of *N*-(1-phenylethyl)-1-(*o*-substituted phenyl)ethanamines **3b**–**e** (Figure 2) in ≥95% diastereomeric excess with good yield (67–97%). Importantly, products **3b**–**e** (see general procedure A and procedures **3b**–**e**, experimental section) could be smoothly converted into the corresponding primary amines in ≥95% ee with good overall yield from the corresponding ketones (58–61%, *ortho*-OMe was 92%).[7] This work represents one of less than a handful of reports on the subject of how to access these hindered (*ortho*-substituted phenyl)ethanamines **4b**–**e** (not shown).



a After one crystallization, yield from starting ketone.

Figure 2 Titanium(IV) isopropoxide based reductive amination of aryl methyl ketones

Concerning methyl alkyl ketone substrates, as the steric bulk of the alkyl substituent is gradually reduced, e.g. from cyclohexyl (**3f**: 98% de) to isobutyl (**3h**: 93% de), high diastereomeric excess is maintained (Figure 3). Further reduction in the steric bulk, e.g., to the 2-phenylethyl moiety (product **3i**, Figure 3) resulted in good diastereomeric excess (80% de), and yet further reduction, e.g. to an *n*-hexyl substituent, led to mediocre diastereoselectivity (**3j**: 72% de). All of these products **3f**–**j** were synthesized using general procedure B (experimental section). Within this substrate category, alkyl methyl ketones, only pinacolone (*tert*-butyl methyl ketone) failed to provide the desired product under the standard reaction conditions (general procedure B). This limitation was overcome by replacing the Raney nickel hydrogenation catalyst with Pt/C, allowing formation of amine **3k** with 87% de (Figure 3).

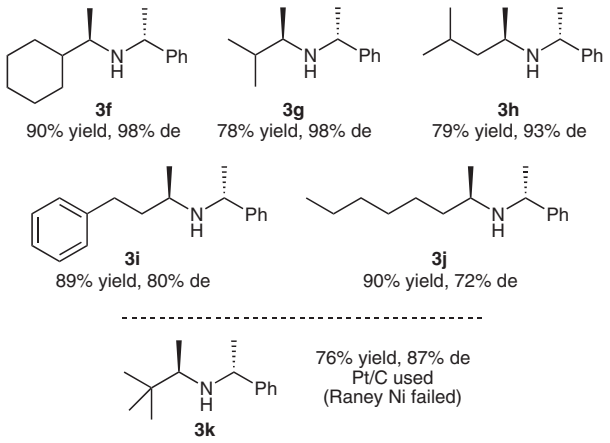
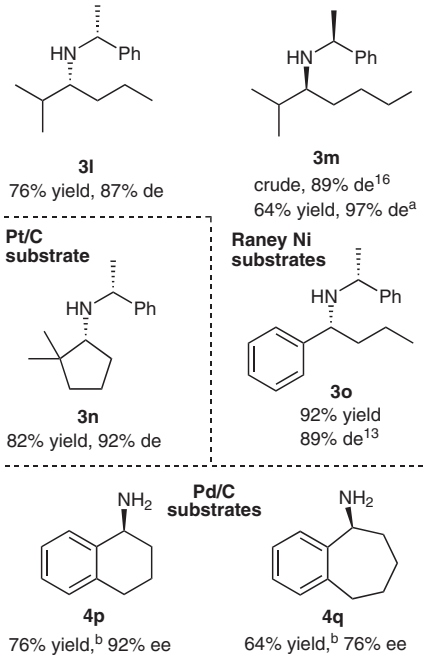


Figure 3 Titanium-based reductive amination of alkyl methyl ketones

The following conclusions can be drawn and used to predict the diastereoselectivity of yet unexamined alkyl methyl ketone substrates. When the alkyl group contains α- or β-branching high product diastereomeric excess (90–98%) will occur, γ-branching can be expected to provide good diastereomeric excess (~80%), while δ-branching or *n*-alkyl substituents will lead to mediocre diastereomeric excess (~70%). Pinacolone (*tert*-butyl methyl ketone) and similar quaternary carbon bearing methyl ketones, e.g. 1-adamantyl, can be expected to give very good diastereomeric excess (85–90%) when using platinum on carbon as the heterogeneous hydrogenation catalyst.

The prior chiral amine examples (Figures 2 and 3) employed methyl ketone starting materials, but the method can be extended to acyclic or cyclic ketones containing one α-branched and one unbranched carbonyl substituent, and still maintain high diastereomeric excess (85–95%, Figure 4).[7,14,15] For these sterically hindered ketones, elevated reaction temperatures and/or hydrogenation pressures, and/or prestirring of the reaction components before hydrogen are required, see **3l**–**o** and **4p**,**q** (experimental section).[16] Within this category, the cyclic alkyl aryl ketone subcategory, α-tetralone (**1p**) and benzosuberone (**1q**), was unique in that yields of the corresponding secondary amines (**3p** and **3q**, not shown) could not be properly quantified because partial hydrogenolysis, formation of **4p** and **4q**, was always noted during their reductive amination. To ameliorate this problem, the crude reductive amination products of α-tetralone (**1p**) and benzosuberone (**1q**) were hydrogenolyzed to convert their **3**/**4** product mixtures into one primary amine product **4** and then the yields and enantiomeric excesses were determined.



[a] After one crystallization, yield from starting ketone.
[b] Overall yield from starting ketone.

Figure 4 Less frequently examined chiral amines

Note that indan-1-one (five-membered-ring analogue of α-tetralone) was not examined. It is subjectively predicted that the 2-oxo variants of these five-, six-, and seven-membered cyclic ketones, e.g. 2-tetralone, would result in low diastereomeric excesses. It is important to note that no Brønsted acid based reductive amination methods are capable of producing the products given in Figure 4, this will be elaborated shortly.

From the combined body of examples delineated above (Figures 2–4), it is, perhaps, self-evident that increases in the difference in the steric bulk between the two ketone substituents lead to increases in the diastereomeric excess, while small differences in steric bulk between the two ketone substituents lead to low diastereoselectivity. For example, octan-3-one (not shown) provided the secondary amine product with ~15% de, this is not surprising since an ethyl group is being differentiated from an *n*-pentyl group. [Note: the carbanion addition method, discussed shortly, provides a very similar product, **3t**, with 81% de (Figure 7).] Using this combined information, qualitative predictions can be made regarding the titanium(IV) isopropoxide reductive amination method. For example, a ketone bearing one β-branched substituent and one *n*-alkyl substituent, e.g. 2-methylheptan-4-one, can be predicted to give the secondary amine product with 75–80% de. Finally, the titanium-based reductive amination method has been extended to the reductive amination of keto esters (not shown).[5]

The workup for the titanium(IV) isopropoxide reductive amination methods is not trivial and is now discussed. Quenching these reactions with water or aqueous acid (0.5–1.0 M HCl) leads to lower isolated yields, but treatment with aqueous 1.0 M sodium hydroxide overcomes this problem. Thus rigorous stirring under these basic workup conditions are recommended for up to one hour to allow the titanium alkoxide intermediates to collapse to titanium dioxide and in doing so liberate any associated product. For base-sensitive substrates aqueous sodium carbonate can be used,[5] but the stirring period may need to be increased. The produced titanium dioxide (fine particulate) represents a filtration challenge that slows or even stops celite filtrations. For preparations of greater than 10 grams this presents a technical obstacle that would likely prevent large-scale (industrial) applications; a creative solution was recently introduced by the Department of Chemical Development at Boehringer Ingelheim Pharmaceuticals.[17] When working up reactions that employ stoichiometric quantities of titanium(IV) isopropoxide they add inexpensive *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)ethylenediamine (EDTE) to convert all of the titanium species into an organic soluble EDTE–Ti(IV) complex. This allows high-yield recovery and removes the filtration problem. Use of this modified workup is highly recommended when scaling up (>10 g) the reductive amination reactions described here.

Increased Diastereoselectivity: Ytterbium(III) Acetate Based Reductive Amination

Regarding alkyl methyl ketones, we noted earlier that alkyl carbonyl substituents containing no branching or γ- or δ-branching, provided mediocre diastereoselectivity (71–80%). For this niche subset of unhindered alkyl methyl ketones, it was found that replacing titanium(IV) isopropoxide with ytterbium(III) acetate allowed fast reductive aminations with elevated diastereoselectivity (80–89%) (Figure 5 and the experimental section, general procedure C).[18] The most dramatic changes in diastereoselectivity were observed for *n*-alkyl methyl ketones. For example, reductive amination of octan-2-one with ytterbium(III) acetate provided secondary amine **3j** (Figure 5) with 87% de, a 15% unit change in diastereomeric excess versus the titanium(IV) isopropoxide method. It should be noted that the same reductive amination albeit with a Brønsted acid, results in mediocre diastereomeric excess (72%).[18] We speculate that the ytterbium(III) acetate facilitates in situ *cis*-to-*trans* imine isomerization before the reduction occurs. A likely route is via an in situ formed ytterbium-based hemiaminal intermediate that could then undergo: (1) pyramidal inversion at nitrogen, or (2) C–N σ bond rotation (180°), before collapsing to the more stable *trans* imine.[18]

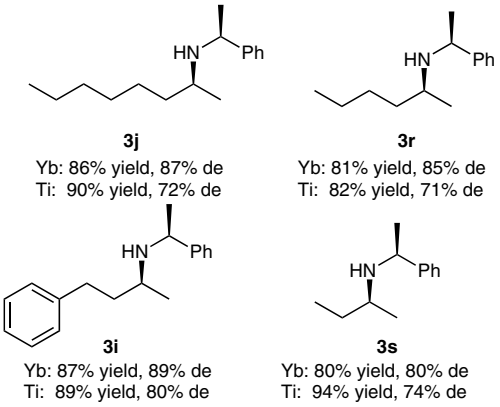


Figure 5 Stoichiometric ytterbium(III) acetate versus titanium(IV) isopropoxide based reductive amination

Brønsted Acid Based Reductive Aminations

Brønsted acid mediated reductive amination with alkan-2-ones occurs under mild conditions: ketone (1.0 equiv), (*R*)- or (*S*)-phenylethylamine (1.1 equiv), acetic acid (20 mol%), methanol, Raney nickel, hydrogen (8 bar), 23 °C.[19] For these unhindered substrates (*n*-alkyl methyl ketones) similar yields and the same diastereomeric excesses are observed when using the titanium(IV) isopropoxide method: ketone (1.0 equiv), (*R*)- or (*S*)-phenylethylamine (1.1 equiv), titanium(IV) isopropoxide (1.25 equiv), various solvents (e.g., hexane, CH_2Cl_2, THF, etc.), Raney nickel, hydrogen (8 bar), 23 °C. The conclusion is that for *n*-alkyl methyl ketones, the most cost-effective and simple method is the Brønsted acid (acetic acid) based method, if products are required with high diastereomeric excess the ytterbium(III) acetate based method should be used.[18]

When the alkyl methyl ketone substrate contains an α- or β-branched alkyl group, the decision becomes more nuanced. For example, using the acetic acid method, isobutyl methyl ketone (4-methylpentan-2-one) requires elevated temperatures (50 °C), and cyclohexyl methyl ketone requires elevated temperatures (50 °C) and increased hydrogen pressure (20 bar) as does acetophenone [H_2 (30 bar), 50 °C] to maintain reasonable yields and reaction times under Brønsted acid catalysis.[19] All of these substrates are reductively aminated with titanium(IV) isopropoxide (1.25 equiv) at 23 °C and using a hydrogen pressure of 8 bar (general procedure A). If the optimized Brønsted acid methods are applied to the starting ketones for the amine products shown in Figure 4, the yields range between 0–25%, regardless of the combination of hydrogen pressure, temperature, and reaction time employed.[19]

In conclusion, the use of titanium(IV) isopropoxide has greatly expanded the possible ketone substrates for reductive amination, while the Brønsted acid methods are restricted to unhindered ketone substrates and always give the same diastereoselectivity as the titanium(IV) isopropoxide method. It is interesting to note that using 10 mol%

ytterbium(III) acetate gives almost identical reaction product profiles as the acetic acid method.[18]

Sequential Reductive Amination–Hydrogenolysis: One-Pot Synthesis of Primary Chiral Amines

Using hydrogen to reduce the in situ formed imine during reductive amination results in a simple question: Can the hydrogenolysis catalyst be added after the reductive amination is complete and permit a one-pot prochiral ketone to chiral primary amine synthesis? To our surprise, prior literature examples of one-pot sequential reductive amination–hydrogenolysis were not found.[20]

Hydrogenolyses are overwhelmingly performed with palladium on carbon in an alcohol solvent, specifically methanol, while our reductive aminations are performed in non-alcoholic solvents [Ti(O*i*-Pr)$_4$ method] or in mixtures thereof [Yb(OAc)$_3$ method]. Regardless, in 2005 we added palladium on carbon at the end of a reductive amination, and under various conditions of catalyst loading, temperature, and hydrogen pressure, we only observed mixtures of the secondary and primary amine products; in short, we failed. In 2010 we noted that hydrogenolysis reactions of secondary amines **3** readily occurred in isopropyl acetate. We then examined isopropyl acetate for its suitability as a reductive amination solvent (reaction rate and diastereoselectivity). Once this was positively confirmed, the one-pot reaction became reasonably trivial to execute, Figure 6 provides the demonstrated examples (general procedure D).[7]

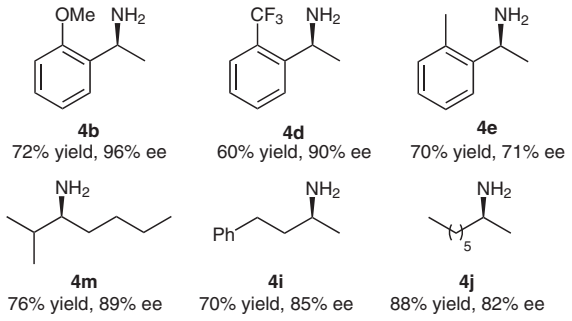


Figure 6 Examples of one-pot chiral amine synthesis

The Carbanion Method: A Complementary Approach to Amine Structures 3

A strong undercurrent in chemistry is the development of more environmentally friendly 'green' methods. In this context, the reductive amination methods outlined above go in the correct direction, e.g., by using only a slight excess (1.1–1.25 equiv) of the nitrogen source, (*R*)- or (*S*)-phenylethylamine, and molecular hydrogen. The carbanion method (Scheme 1) presented here would not be considered green, it requires three equivalents of a dialkylcuprate complex, boron trifluoride etherate, and low reaction temperatures (–78 °C); but the approach does conveniently provide amine structures **3** from prochiral aldehydes **2** in one-pot (Scheme 1 and Figure 7).[21]

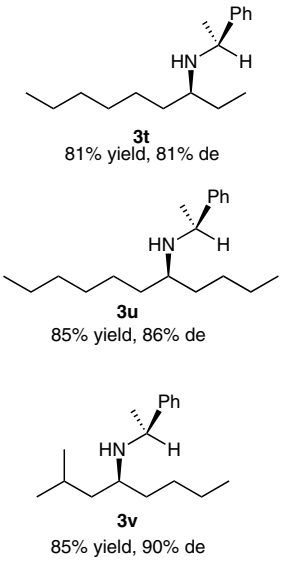
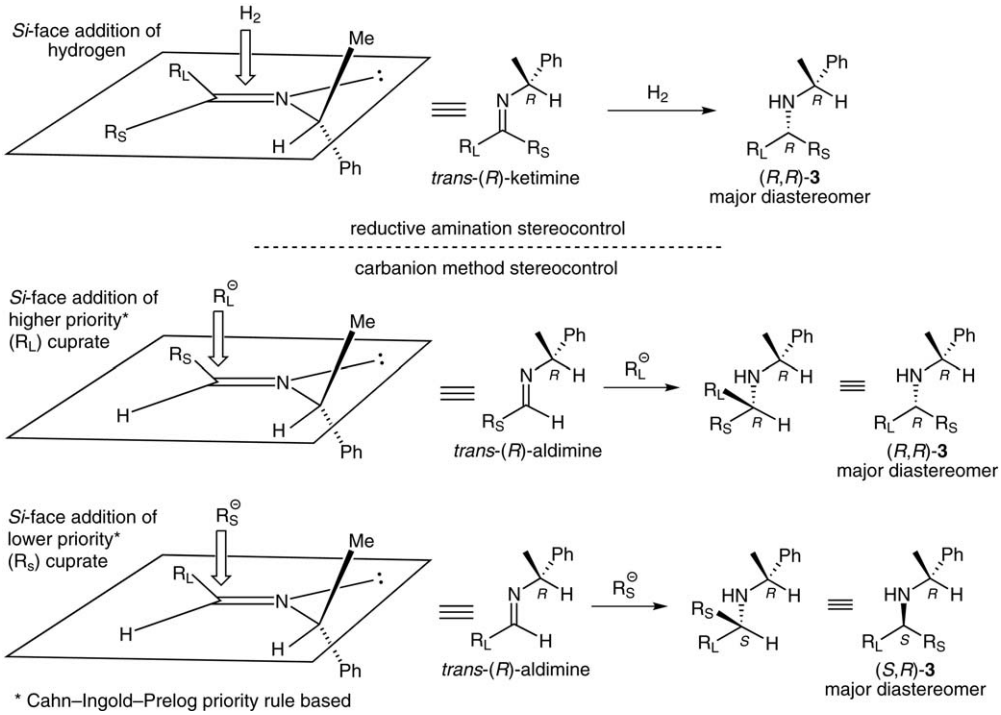


Figure 7 Carbanion-based amine synthesis

All of the acyclic reductive amination products noted in Figures 2–6 can be synthesized using the carbanion method, but it would only make sense to do so when high enantiomeric excess is provided and the reductive amination method simultaneously provides, or can be predicted to provide, low enantiomeric excess (0–70%). We have consequently limited our carbanion discussion to amine structures that cannot be achieved in useful enantiomeric excess via reductive amination, e.g., nonan-3-amine and undecan-5-amine. The carbanion method provides the precursor secondary amines **3t** and **3u** for these primary amines with good diastereomeric excess (81% and 86%, respectively, Figure 7). The diastereoselectivity noted for structure **3v** (90% de, Figure 7) would be predicted to exceed that via reductive amination.[22] General procedure E describes the synthesis of **3t**, **3u**, and **3v**.[21]

The conclusion here is that good-to-high diastereomeric excess can be achieved when only small differences in the steric bulk exist between the two α-substituents, e.g. in **3u** (Figure 7) between an *n*-hexyl and an *n*-butyl moiety. This contrasts dramatically with the reductive amination method which would provide essentially no diastereoselectivity. The outlined carbanion addition method should also be amenable to the use of arylcuprates. If correct, this would be important because high diastereomeric excess could be obtained for a difficult to access category of chiral amines, i.e., those with two large α-substituents. For example, two different aromatic moieties (one from the cuprate and one from an aromatic aldehyde) could represent R_L and R_S in Scheme 3.



Scheme 3 Stereocontrol: reductive amination and carbanion addition methods

Stereocontrol (Reductive Amination and Carbanion Addition)

For both the reductive amination and carbanion addition methods, the stereocontrol is dictated by the geometry of the in situ formed chiral ketimine (reductive amination) or aldimine (carbanion addition) intermediates (Scheme 3). The ketimines will exist predominately in the *trans* form and hydrogen will add from the face containing the methyl group of the auxiliary. As the steric bulk between the two carbonyl substituents (starting reductive amination ketone) becomes less pronounced, more of the *cis* isomer (not shown) will be present, and lower diastereomeric excess will result for the secondary amines **3**. For the aldimines, the *trans* form is expected to dominate regardless of the alkyl or aryl moiety residing on the starting aldehyde, and the carbanion will attack from the less hindered 'methyl' face. A second, but subordinate, factor influencing the stereoselectivity of carbanion addition is the steric bulk of the carbanion. Increasing the size of the carbanion results in increased diastereoselectivity. It is readily appreciated that using the carbanion method, either diastereomer of the secondary amine **3** can be selectively formed as the major product using only one configuration of the auxiliary. This is accomplished by switching whether the carbanion or the carbonyl substituent on the starting aldehyde is R_L or R_S as noted in Scheme 3.

Conclusion

Forward-looking methods for chiral amine synthesis are currently being developed,[1] but until optimized and technically simple methods are produced, the chiral amine methods offered here will be valuable because of their reaction step-efficiency, simplicity, exclusive use of commercially available catalysts and reagents, and robustness.

This summary was written to provide an overall perspective of the strengths and weaknesses of the presented methods, and Figure 1 and Scheme 1 provide the overall strategy and accessible amine categories. This should enable researchers with short timelines (number of reaction steps and overall yield of lower importance: medicinal chemists) or those requiring step-efficiency (number of reaction steps and overall yield of high importance: process research chemists) to reach quick project decisions regarding the applicability, or lack thereof, for the presented methods.

The cumulative examples shown here (Figure 2–6) demonstrate that greatly increased substrate breath (and at times stereoselectivity) can now be achieved, and this represents a significant advance for the general field of reductive amination. With this perspective, reductive amination should find a greater role in the design of natural products and pharmaceutical drugs, and we have already implemented these methods to access new organocatalyst templates.[23] Finally, where reductive amination substrate limitations exist, the carbanion approach may be a valuable alternative.

General procedures A–E and procedures for **3a**–**e**,**i**,**k**–**o**,**r**,**s**–**v** and **4b**,**d**,**e**,**i**,**j**,**m**–**p** are detailed below. Please note the chiral auxiliary used here is invariably referred to as (*R*)- or (*S*)-phenylethylamine or (*R*)- or (*S*)-α-methylbenzylamine (α-MBA). Compounds that were excluded are synthesized using the general methods as noted in the discussion section of this manuscript. Please note that all

compounds discussed here have been previously described and characterized by either our group or other research groups. We characterized the following for the first time: **3k**, **3l**, **3n**, **3o**, **3t**, **3u**, **3v**, **4p** (trifluoroacetamide), **4q** (trifluoroacetamide). When we were not the first group to characterize a compound, we nonetheless have provided the ^{1}H NMR text data (and often, but not always, the ^{13}C NMR text data) and have always included a copy of the chromatographic (HPLC or GC) data and the NMR spectra in the supporting information of the original manuscripts.

Titanium(IV) Isopropoxide Based Reductive Amination; General Procedure A

In an anhydrous solvent (0.50–0.83 M), a prochiral ketone **1** (2.50–5.00 mmol), Ti(O*i*-Pr)$_4$ (1.25 equiv), and (*R*)- or (*S*)-α-MBA (1.10 equiv) were combined and stirred at r.t. for 30 min at r.t. A heterogeneous catalyst, Raney Ni [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 with H_2 [120 psi (8.3 bar)] and stirred at r.t. At complete conversion (<4.0 area% of ketone and imine by GC, see specific products for exact reaction times), the mixture was worked up by transferring it to an Erlenmeyer flask with EtOAc (~50 mL) or CH_2Cl_2 (~50 mL) and rigorously stirring it with aq 1.0 M NaOH (20 mL) for 1 h. [For an alternative workup allowing scale-up beyond 15 g, see ref.[17]]. The heterogeneous mixture was then filtered through a bed of celite and the celite subsequently washed with EtOAc or CH_2Cl_2. The filtrate was concentrated (rotary evaporator bath temperature ≤ 25 °C) to remove the low boiling organics and the remaining aqueous soln was then extracted with CH_2Cl_2 (3 × 15 mL). Note: the temperature of the rotary evaporator bath was maintained at or below 25 °C when working with the free amine products **3** to suppress the loss (yield reduction) of these semi-volatile compounds. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated (rotary evaporator bath, T ≤ 25 °C). Diastereomeric excesses were then determined by analysis of the crude product. The isolated yield of the combined diastereomers was determined after flash chromatography using the following protocol. Due to the high volatility of some of the amine products **3**, the desirable column fractions were combined in a round-bottom flask and aq 4.0 M HCl (~3.0 equiv) was added. After brief but vigorous stirring (<10 min), the soln of amine diastereomeric hydrochloride salts was rotary evaporated (rotary evaporator bath can now be as high as 50 °C because the amine salts are not volatile). The resulting solid or viscous liquid was high vacuum dried until a constant weight was achieved. The major diastereomer, (*R*,*R*) or (*S*,*S*), was isolated in pure form only after further careful flash chromatography of the free amine diastereomeric mixture.

Titanium(IV) Isopropoxide Based Reductive Amination; General Procedure B

General procedure A was used, with the following refined points: Heterogeneous hydrogenation catalyst: Raney Ni (70–100 wt%); anhydrous solvent: hexane, CH_2Cl_2, THF, or *t*-BuOMe; reaction times: 6–11 h.

Reductive Amination with Stoichiometric Ytterbium(III) Acetate; General Procedure C

In a dry reaction vessel, Yb(OAc)$_3$ (0.96 g, 2.75 mmol, 1.1 equiv) was added and subsequently evacuated under high vacuum for 5 min before flooding with N_2, anhyd MeOH (2.5 mL, 1.0 M) was then added. To this soln a prochiral ketone **1** (2.5 mmol, 1.0 equiv) and (*S*)-α-MBA (0.35 mL, 2.75 mmol, 1.1 equiv) were added and the mixture was subsequently stirred at r.t. for 20–30 min. A THF slurry of Raney Ni [100 wt% based on the ketone, pre-triturated with EtOH (3 ×) and then with anhyd THF (3 ×) before addition] was transferred to the mixture using anhyd THF (2.5 mL, final molarity of reaction soln was 0.5 M) and the reaction vessel was pressurized with H_2 [120 psi (8.3 bar)]. After 12 h at 22 °C, <3 area% of the ketone and imine intermediate remained by GC analysis, and the mixture was then diluted with MeOH (15 mL), filtered through a bed of celite, and the celite subsequently washed with MeOH (3 × 15 mL). The combined filtrates were then evaporated to dryness (rotary evaporate at ≤25 °C for short periods due to the semi-volatile nature of the secondary amine products **3**), and $CHCl_3$ (20 mL) and aq 1.0 M NaOH (15 mL) were added and this mixture stirred for 90 min. After transferring to a separatory funnel, the $CHCl_3$ layer was removed, and the aqueous layer further extracted with $CHCl_3$ (3 × 15 mL). The combined $CHCl_3$ extracts were filtered through a small bed of celite (removes turbidity) and the celite subsequently washed with $CHCl_3$ (2 × 15 mL). The filtrate was then washed with sat. NH_4Cl (2 × 20 mL) [removes residual small quantities of α-MBA], then with brine (1 × 20 mL), dried ($MgSO_4$), 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 chromatography (silica gel) was performed as noted in general procedure A.

Pretreatment of Yb(OAc)$_3$

After using several bottles of Yb(OAc)$_3$, which is sold and described as a semihydrate (Sigma-Aldrich catalog no. 544973), we noted that it was sometimes free-flowing while other bottles from the same production lot were not. As a consequence, before using Yb(OAc)$_3$ for any of our research, 10-gram quantities were first high vacuum dried at 80 °C to constant weight (~12 h). Yb(OAc)$_3$ treated in this way was used for the optimal results shown in general procedures C and D. The dried Yb(OAc)$_3$ could be stored in a dry screw cap glass bottle at r.t., and this container could be repeatedly opened to the atmosphere for short periods of time (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.

One-Pot Synthesis of Enantioenriched Primary Amines; General Procedure D

In a reaction vessel under N_2, Yb(OAc)$_3$ (2.2 mmol, 1.1 equiv) [see note about Yb(OAc)$_3$ as found in general procedure C] or Ti(O*i*-Pr)$_4$ (2.4 mmol, 1.2 equiv) was added, followed by the solvent (2.0 mL, 1.0 M), ketone (2.0 mmol, 1.0 equiv), and (*S*)-phenylethylamine (2.4 mmol, 1.2 equiv). This was stirred for 30 min, at r.t., and then a reaction solvent slurry (2.0 mL) of Raney Ni [100 wt% based on the ketone, triturated first with EtOH (3 × 2 mL) and then with the reaction solvent (3 × 2 mL)] was added. Alternatively, when Pd/Al_2O_3 (1.5 mol%) was the heterogeneous hydrogenation catalyst, additional reaction solvent (2.0 mL) was added because a slurry was not used to add the Pd/Al_2O_3. [For clarity: the final molarity for all reactions was 0.5 M. Note: all hydrogenation catalyst wt% or mol% numbers are based on the starting ketone.] The reaction vessel was then pressurized with H_2 (10–20 bar) at 24 °C, 35 °C, or 50 °C, depending on the specific substrate, with stirring. After stirring for 12–48 h, <4 area% of the ketone substrate and imine intermediate (combined) remained by GC analysis, and Pd/C (1.0 mol%) or Pd(OH)$_2$ (1.0 mol%) was added. The reaction was then heated at 50 or 55 °C under H_2 (20 bar). Importantly, the reaction was worked up when 5–6 area% of the secondary amine starting material still remained, which was most often at 48 h. Workup: dilute with EtOAc (40 mL) and add aq 1.0 M NaOH (30 mL). After vigorous stirring for 4 h in a septa-capped Erlenmeyer flask, the heterogeneous two-phase soln was filtered through a bed of celite, and the celite subsequently washed with EtOAc (3 × 10 mL). [Note: the primary amines are semi-volatile to volatile, do not aspirate the filtration step more than required.] The aqueous layer was further extracted with EtOAc (3 × 20 mL), and the combined organic layers were then treated with aq 4.0 M HCl (~4 equiv). This was concentrated until a volume of ~0.5 to 1.0 mL and generally had a yellow color. If the chemical purity of the product was not >95 area% (GC), then extractive purification with $CHCl_3$ and CH_2Cl_2 was helpful. Distilled H_2O (50 mL) and $CHCl_3$ (50 mL) were added and the $CHCl_3$ layer was further extracted with distilled H_2O (2 × 10 mL). To the combined aqueous layers, CH_2Cl_2 (50 mL) was added, and then the aqueous phase was made strongly basic with NaOH (pH >11) with

4.0 M NaOH. After removal of the CH_2Cl_2 layer, the basic aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL). To the combined CH_2Cl_2 layers was added aq 4.0 M HCl (~3 equiv) and this was concentrated (rotary evaporator, bath temperature initial: 30 °C; final: ~70 °C) providing an off-white solid that was dried under high vacuum until a constant weight was achieved (usually overnight). To assess the enantiomeric excess of the product, a sample of the primary amine HCl salt (1 mmol) was neutralized (aq NaOH–EtOAc) and then converted into the corresponding trifluoroacetamide, analysis using GC allowed the enantiomeric excess to be determined.

Bis[(*R*)-1-phenylethyl]amine (3a)
Following general procedure A using EtOAc (5.0 mL, 0.5 M), Ti(O*i*-Pr)$_4$ (3.13 mmol, 1.25 equiv), acetophenone (**1a**, 2.50 mmol, 1.0 equiv), (*S*)-α-MBA (2.75 mmol, 1.1 equiv), Raney Ni (300 mg, 100 wt%); H_2 (8.3 bar), 24 °C, 8 h. Flash chromatography (EtOAc–heptane–NH_4OH, 25:74:1) gave the mixture of diastereomers (480 mg, 85%, 95% de) as a colorless viscous oil. GC methods and product retention times are available.[14]

(*R*,*R*)-3a
Previously characterized; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.35 (m, 10 H), 3.49 (q, *J* = 6.6 Hz, 1 H), 1.55 (br s, 1 H), 1.27 (d, *J* = 6.6 Hz, 6 H).

(*S*)-1-(2-Methoxyphenyl)-*N*-[(*S*)-1-phenylethyl]ethanamine (3b)
Following general procedure A using *i*-PrOAc, Ti(O*i*-Pr)$_4$ (4.75 mmol, 1.25 equiv), 1-(2-methoxyphenyl)ethanone (**1b**, 3.0 mmol, 1.0 equiv), (*S*)-α-MBA (3.3 mmol, 1.1 equiv), Raney Ni (100 wt%); H_2 (10 bar), 24 °C, 16 h. After workup and high vacuum drying, the product was determined to be of high chemical purity (GC and ^{1}H NMR, ≥95%), no column chromatography or crystallization was required; yield: 97%; 98% de. GC methods and product retention times are available.[7]

(*S*,*S*)-3b
Previously characterized; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–6.8 (m, 9 H), 3.77 (m, 4 H), 3.54 (q, *J* = 6.6 Hz, 1 H), 2.18 (br, 1 H), 1.32 (d, *J* = 6.7 Hz, 3 H), 1.29 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 146.1, 133.5, 128.3, 128.0, 127.6, 126.9, 126.7, 120.7, 110.8, 55.4, 55.2, 51.6, 25.3, 22.9.

(*R*,*S*)-3b
Minor diastereomer; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3–6.8 (m, 9 H), 4.1 (q, *J* = 6.8 Hz, 1 H), 3.77 (s, 3 H), 3.69 (q, *J* = 6.7 Hz, 1 H), 1.65 (br, 1 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.33 (d, *J* = 6.7 Hz, 3 H).

(*S*)-*N*-[(*S*)-1-(2-Fluorophenyl)ethyl]-1-phenylethanamine (3c)

Pt/C Results
Following general procedure A using *i*-PrOAc, Ti(O*i*-Pr)$_4$ (2.5 mmol, 1.25 equiv), *o*-fluoroacetophenone (**1c**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.2 mmol, 1.1 equiv), Pt/C (0.5 mol%); H_2 (20 bar), 35 °C, 24 h. Crude product (40% de) and the defluorinated compound, <0.80 area% (GC), was noted. Crude product **3c** was purified via crystallization with phthalic acid (1.0 equiv) in *i*-PrOH (6 volumes), providing **3c** phthalic acid salt; yield: 56% (from **1c**); 99% de (GC). More details regarding the crystallization and the GC methods and product retention times are available.[7]

Raney Ni Results
Following general procedure A using *i*-PrOAc, Ti(O*i*-Pr)$_4$ (2.5 mmol, 1.25 equiv), *o*-fluoroacetophenone (**1c**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.2 mmol, 1.1 equiv), Raney Ni (100 wt%); H_2 (20 bar), 35 °C, 24 h. Crude product (97% de); from multiple reactions we noted the defluorinated byproduct was present in 6–10 area% (GC). Purification by flash chromatography (silica gel, hexanes–EtOAc–NH_4OH, 83:15:2); yield: 79%. Attempts to crystallize this crude product failed because the defluorinated byproduct could not be fully removed. GC methods and product retention times are available.[7]

(*S*,*S*)-3c
Previously characterized; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3–7.0 (m, 9 H), 3.76 (q, *J* = 6.7 Hz, 1 H), 3.51 (q, *J* = 6.6 Hz, 1 H), 1.62 (br s, NH, 1 H), 1.31 (d, *J* = 6.7 Hz, 3 H), 1.28 (d, *J* = 6.7 Hz, 3 H).

(*S*,*S*)-3c·Phthalic Acid Salt
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.5–6.9 (m, 13 H), 4.45 (q, *J* = 6.7 Hz, 1 H), 4.12 (q, *J* = 6.6 Hz, 1 H), 1.81 (d, *J* = 6.8 Hz, 3 H), 1.75 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = = 171.8, 161.4, 158.9, 136.4, 134.2, 133.5, 131.4, 130.7, 130.6, 129.3, 129.1, 128.1, 125.4, 124.5, 124.3, 121.5, 116.0, 115.8, 57.5, 49.5, 49.4, 21.2, 20.8.

(*S*)-1-Phenyl-*N*-{(*S*)-1-[2-(trifluoromethyl)phenyl]ethyl}ethanamine (3d)
Following general procedure A using *i*-PrOAc, Ti(O*i*-Pr)$_4$ (3.2 mmol, 1.6 equiv), 1-[2-(trifluoromethyl)phenyl]ethanone (**1d**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.4 mmol, 1.2 equiv), Pd/Al_2O_3 (1.5 mol%); H_2 (15 bar), 35 °C, 24 h. Crude product: 88% de (^{1}H NMR). Crude product was purified via crystallization with phthalic acid (1.0 equiv) in *i*-PrOH (4 volumes) and heptane (4 volumes); yield: 73% (from **1d**); >99% de (^{1}H NMR). GC analysis did not allow separation of these diastereomers. Further product information is available.[7]

(*S*,*S*)-3d
Previously characterized; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.9–7.2 (m, 9 H), 4.07 (q, *J* = 6.4 Hz, 1 H), 3.49 (q, *J* = 6.7 Hz, 1 H), 1.68 (br, 1 H), 1.24 (d, *J* = 6.7 Hz, 6 H).

(*S*,*S*)-3d·Phthalic Acid Salt
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.5–7.3 (m, 13 H), 4.55 (q, *J* = 6.5 Hz, 1 H), 4.23 (q, *J* = 6.7 Hz, 1 H), 1.79 (d, *J* = 6.8 Hz, 3 H), 1.73 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 136.7, 134.1, 133.5, 131.4, 129.3, 129.2, 128.6, 128.5, 127.8, 57.8, 53.0, 22.6, 21.7.

(*S*)-*N*-[(*S*)-1-(2-Methylphenyl)ethyl]-1-phenylethanamine (3e)
Following general procedure A using *i*-PrOAc, Ti(O*i*-Pr)$_4$ (3.2 mmol, 1.6 equiv), 1-(2-methylphenyl)ethanone (**1e**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.4 mmol, 1.2 equiv), Pd/Al_2O_3 (1.5 mol%); H_2 (15 bar), 35 °C, 24 h. Crude product: 74% de. The crude product was purified via crystallization with phthalic acid (1.0 equiv) in *i*-PrOH (3 volumes) and heptane (4 volumes); yield: 67% (from **1e**); 95% de (GC). A second crystallization provided; yield: 48% (from **1e**); 99% de. GC methods and product retention times are available.[7]

(*S*,*S*)-3e
Previously synthesized; free base.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5–7.0 (m, 9 H), 3.78 (q, *J* = 6.7 Hz, 1 H), 3.50 (q, *J* = 6.8 Hz, 1 H), 1.98 (s, 3 H), 1.65 (br, 1 H), 1.32 (d, *J* = 6.4 Hz, 3 H), 1.22 (d, *J* = 6.5 Hz, 3 H).

(*S*,*S*)-3e·Phthalic Acid Salt
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.37 (br, 2 H), 8.5–7.0 (m, 13 H), 4.30 (q, *J* = 6.3 Hz, 1 H), 4.14 (q, *J* = 6.4 Hz, 1 H), 1.81 (d, *J* = 6.8 Hz, 3 H), 1.70 (d, *J* = 6.8 Hz, 3 H), 1.53 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 136.7, 135.9, 135.5, 134.3, 133.5, 131.4, 130.9, 129.3, 129.1, 128.4, 128.2, 127.5, 126.3, 57.0, 52.4, 21.3, 21.2, 18.5.

(2*R*)-3,3-Dimethyl-*N*-[(*R*)-1-phenylethyl]butan-2-amine (3k)
Following general procedure B using pinacolone (**1k**, 5.00 mmol), (*R*)-α-MBA, (1.10 equiv), and Ti(O*i*-Pr)$_4$ (1.25 equiv) was prestirred for 2 h (neat), then hexane (6.0 mL, 0.83 M) and Pt/C (60 mg, 0.3 mol%) [added in 3 equal portion, thus Pt/C (20 mg) at t = 0 h, 3 h, and 6 h] (20 mg) were added and pressurized with H_2 [120 psi (8.3 bar)]; 50 °C. Reaction time: 20 h. Crude product: 87% de. Flash chromatography (cyclohexane–EtOAc–NH_4OH, 95:1:4) gave a mixture of diastereomers as a colorless viscous oil; yield: 0.78 g (76%). The major diastereomer was separately obtained by further flash chromatography using the same eluent system. GC methods and product retention times are available.[14]

(*R*,*R*)-3k
Free base; R_f = 0.47 (cyclohexane–EtOAc–NH_4OH, 91:6:3).

IR (KBr): 3427 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.36 (m, 5 H), 3.77 (q, *J* = 6.5 Hz, 1 H), 2.29 (q, *J* = 6.5 Hz, 1 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 0.84–0.89 (m 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 128.2, 126.7, 126.6, 59.5, 57.0, 34.7, 26.5, 23.6, 15.9.

MS (EI): *m*/*z* (%) = 205.1 (M^+, 16), 190.1 (24), 148.1 (76), 105.1 (100), 86.1 (12), 77, (8), 44 (52).

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.65; H, 11.13; N, 6.87.

(3*R*)-2-Methyl-*N*-[(*R*)-1-phenylethyl]hexan-3-amine (3l)
A mixture of 2-methylhexan-3-one (**1l**, 4.15 mL, 30.00 mmol, 1.00 equiv), (*R*)-α-MBA (4.07 mL, 31.5 mmol, 1.05 equiv), and Ti(O*i*-Pr)$_4$ (97% grade, 26.6 mL, 90.0 mmol, 3.00 equiv) in anhyd DCE (20 mL) was stirred at 900 rpm under argon at 40 °C for 2 h. Raney Ni (2.8 g) suspended in DCE (10 mL) was added and this was hydrogenated at 120 psi (8.3 bar) with vigorous stirring (1200 rpm) at 60 °C. After 24 h, 13 area% of the starting material remained, and after 35 h (3 area% of the starting material remaining) the mixture was quenched with aq 2.5 M NaOH (30 mL). After stirring for 2 h, the soln was diluted with CH_2Cl_2 (50 mL), filtered through celite, and the celite was washed with CH_2Cl_2 (3 × 70 mL). The organic layer was removed from the filtrate and the aqueous layer further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness and kept under high vacuum to remove excess (*R*)-α-MBA. The resulting oil, secondary amine **3l**, was then treated with 4.0 M ethereal HCl (15 mL), filtered, and dried to afford **3l**·HCl; yield: 5.82 g (76%); 87% de).

For a small-scale example, details of chromatography (silica gel), GC methods, and product retention times are available.[15]

(*R*,*R*)-3l
Free base; R_f = 0.51 (cyclohexane–EtOAc–NH_4OH, 90:6:4) [minor diastereomer (*S*,*R*)-**3l**, R_f = 0.40].

IR (KBr): 3432, 2957, 1462, 1360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.38 (m, 5 H), 3.84 (q, *J* = 6.5 Hz, 1 H), 2.16 (m, 1 H), 1.86 (m, 1 H), 1.26 (d, *J* = 6.5Hz, 3 H), 1.13 (m, 4 H), 0.85 (m, 3 H), 0.78 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 128.1, 126.7, 126.6, 58.7, 55.0, 32.4, 28.8, 24.8, 19.6, 18.9, 16.7, 14.2.

MS (EI): *m*/*z* (%) = 218 (6) [M^+], 205 (18), 204 (62), 105 (100), 72 (79).

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 82.01; H, 11.40; N, 6.51.

(*S*)-2-Methyl-*N*-[(*S*)-1-phenylethyl]heptan-3-amine (3m)
Reaction details: Ti(O*i*-Pr)$_4$ (6.0 mmol, 3.0 equiv), 2-methylheptan-3-one (**1m**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.4 mmol, 1.2 equiv) were prestirred neat at 50 °C for 4 h. [Note: *this prestirring at elevated temperature was inadvertently dropped from the original experimental description*[7]*, but it is absolutely required and is consistent with our earlier description*[15] *for a similar substrate* (***3l***).] DCE (2 mL) was then added followed by a toluene (2 mL) slurry of Raney Ni (100 wt%). [Note: the DCE allows high de to be achieved, but this solvent did not allow a free-flowing slurry of Raney Ni. After our earlier literature description for **3l**, we found that a toluene slurry of Raney Ni was excellent for transferring the Raney Ni (large-gauge needle/syringe) and importantly did not lower the de. Use of toluene as the sole reaction solvent resulted in reduced de.] Pressurize with H_2 (20 bar), 50 °C, 48 h. Crude product: 89% de (GC). The crude product was converted into **3m**·HCl and crystallized (cyclohexane, 16 volumes); yield: 64% (from **1m**); 97% de (GC). GC methods and product retention times are available.[7]

(*S*,*S*)-3m
Free base; R_f = 0.50 (hexanes–EtOAc–NH_4OH, 90:8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 5 H), 3.84 (q, *J* = 6.6 Hz, 1 H), 2.15 (m, 1 H), 1.87 (m, 1 H), 1.36–1.05 (m, 10 H), 0.87–0.79 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 128.2, 126.7, 126.6, 59.0, 55.2, 29.9, 29.0, 28.7, 24.8, 22.8, 18.9, 16.9, 14.0.

(1*R*)-2,2-Dimethyl-*N*-[(*R*)-1-phenylethyl]cyclopentanamine (3n)
The reaction was prepared according to general method A with the following noted refinements: ketone **1n** (5.00 mmol) prestirred for 3 h (neat) with (*R*)-α-MBA and Ti(O*i*-Pr)$_4$; then EtOH (6.0 mL, 0.83 M) was added; H_2 [120 psi (8.3 bar)]; Pt/C (60.0 mg, 0.3 mol%) [added in 4 equal portion, thus Pt/C (15 mg) at t = 0 h, 2 h, 4 h, and 8 h]; 50 °C. Reaction time: 20 h. Crude product: 92% de. Purification by column chromatography (cyclohexane–EtOAc–NH_4OH, 88:10:02) provided the mixture of diastereomers as a colorless viscous liquid, which was then converted into the HCl salt; yield: 1.04 g (82%). The analytically pure major (*R*,*R*)-**3n** diastereomer was obtained by further column chromatography (cyclohexane–EtOAc–NH_4OH, 90:8:2) of the diastereomeric free amine mixture. GC methods and product retention times are available.[14]

(*R*,*R*)-3n
Free base; R_f = 0.64 (cyclohexane–EtOAc–NH_4OH, 75:20:5) [minor diastereomer (*S*,*R*)-**3n**: R_f = 0.50].

IR (KBr): 3441, 2955, 2864, 1465, 1134, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 3.86 (q, *J* = 6.4 Hz, 1 H), 2.53 (m, 1 H), 1.78–1.33 (m, 6 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 1.02 (s, 3 H), 0.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 128.2, 126.7, 126.6, 65.6, 57.2, 40.9, 39.9, 32.0, 28.1, 24.6, 21.1, 19.7.

MS (EI): *m*/*z* (%) = 217 (22) [M^+], 202 (54), 160 (58), 146 (10), 105 (100), 56 (26).

Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 83.04; H, 10.57; N, 6.50.

(1*R*)-1-Phenyl-*N*-[(*R*)-1-phenylethyl]butan-1-amine (3o)
Reaction details: The reaction was prepared according to general method A with the following noted refinements: ketone **1o** (5.00 mmol), (*R*)-α-MBA, and Ti(O*i*-Pr)$_4$ prestirred for 2 h in EtOAc (10.0 mL, 0.5 M). Raney Ni (500 mg, 100 wt%) was added, pressurized with H_2 (8.3 bar), and heated at 35 °C, reaction time: 15 h. We originally reported a 94% de for this product[14] but all subsequent research on this product (by our group) has shown this is not the case and we have observed a range of de (84–94%), see ref. 13 for more details. The mixture of diastereomers was isolated as a colorless viscous liquid; yield: 1.17 g (92%). An analytically pure sample of the (*R*,*R*)-**3o** diastereomer was obtained by repeated recrystallization of the HCl salt of the diastereomeric mixture

(hexane–EtOH). GC methods and product retention times are available.[14]

(*R*,*R*)-3o
Free base; R_f = 0.60 (cyclohexane–EtOAc–NH_4OH, 15:83:02).

IR (KBr): 3445, 2958, 1602, 1492, 1453, 1368, 1125, 761, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 10 H), 3.47 (q, *J* = 6.4 Hz, 1 H), 3.28 (t, *J* = 6.8 Hz, 1 H), 1.60 (m, 2 H), 1.51 (m, 1 H), 1.24 (d, *J* = 6.8 Hz, 3 H), 1.08 (m, 1 H), 0.77 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100MHz, $CDCl_3$): δ = 145.8, 144.9, 128.3, 128.25, 127.2, 126.7, 59.8, 54.8, 41.0, 25.1, 19.6, 14.0.

MS (EI): *m*/*z* (%) = 253 (4) [M^+], 238 (25), 210 (100), 105 (86), 91 (33), 77 (14).

Anal. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53. Found: C, 84.75; H, 9.24; N, 5.48.

(*S*)-1-(2-Methoxyphenyl)ethanamine (4b)
Following general procedure D. Reductive amination stage: *i*-PrOAc (4.0 mL, 0.5 M), 1-(2-methoxyphenyl)ethanone (**1b**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.4 mmol, 1.2 equiv), Ti(O*i*-Pr)$_4$ (2.4 mmol, 1.2 equiv), stirred for 20 min, then Raney Ni (100 wt%) was added, pressurized with H_2 (10 bar), 24 °C, 24 h. Hydrogenolysis stage: Open reactor, Pd/C (1.0 mol%) was added, then pressurized with H_2 (20 bar), 48 h, 55 °C. Acid-base workup (see general procedures) and conversion into the hydrochloride salt gave **4b**·HCl; yield: 72%. The high chemical purity was confirmed by GC (a small portion was converted into the free amine and shown to be >95% pure (GC). GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4b·HCl
Previously characterized.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.61 (br, 3 H), 7.4–6.8 (m, 4 H), 4.68 (q, *J* = 6.8 Hz, 1 H), 3.81 (s, 3 H), 1.68 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 130.1, 127.7, 125.7, 121.0, 110.7, 55.6, 47.3, 18.6.

(*S*)-1-[2-(Trifluoromethyl)phenyl]ethanamine (4d)
Following general procedure D. Reductive amination stage: *i*-PrOAc (6.0 mL, 0.5 M), 2′-(trifluoromethyl)acetophenone (**1d**, 3.0 mmol, 1.0 equiv), (*S*)-α-MBA (3.6 mmol, 1.2 equiv), Ti(O*i*-Pr)$_4$ (4.8 mmol, 1.6 equiv), stirred for 20 min, then Pd/Al_2O_3 (1.5 mol%) was added, pressurized with H_2 (20 bar), 35 °C, 24 h. Hydrogenolysis stage: Open reactor, $Pd(OH)_2$ (1.0 mol%) was added, then pressurized with H_2 (20 bar), 50 °C, 48 h. Acid-base workup (see general procedures) and conversion into the hydrochloride salt gave **4d**·HCl; yield: 60%. The high chemical purity was confirmed by GC analysis of the free amine, >98% purity. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4d·HCl
Previously characterized.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.93 (br, 3 H), 8.0–7.4 (m, 4 H), 4.83 (br, 1 H), 1.71 (br, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 133.1, 129.0, 127.9, 127.8 (q), 126.3, 124.0 (q), 42.5, 21.7.

(*S*)-1-(2-Methylphenyl)ethanamine (4e)
Following general procedure D. Reductive amination stage: *i*-PrOAc (6.0 mL, 0.5 M), 1-(2-methylphenyl)ethanone (**1e**, 3.0 mmol, 1.0 equiv), (*S*)-α-MBA (3.6 mmol, 1.2 equiv), Ti(O*i*-Pr)$_4$ (4.8 mmol, 1.6 equiv), stirred 20 min, then Pd/Al_2O_3 (1.5 mol%) was added, pressurized with H_2 (20 bar), 35 °C, 36 h. Hydrogenolysis stage: Open reactor, $Pd(OH)_2$ (1.0 mol%) was added, then pressurized with H_2 (20 bar), 55 °C, 48 h. Acid-base workup (see general procedures) and conversion into the hydrochloride salt gave **4e**·HCl; yield: 70%. The high chemical purity was confirmed by GC analysis of the free amine, >96% purity. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4e·HCl
Previously characterized.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (br, 3 H), 7.6–7.1 (m, 4 H), 4.63 (br, 1 H), 2.35 (s, 3 H), 1.62 (br d, 3 H).

(*S*)-4-Phenylbutan-2-amine (4i)
Following general procedure D. Reductive amination stage: $Yb(OAc)_3$ (2.2 mmol, 1.1 equiv) [see pretreatment procedure at the end of general method C], anhyd MeOH (2.0 mL, 1.0 M), anhyd THF [2.0 mL, 1.0 M (used for Raney Ni transfer)], 4-phenylbutan-2-one (**1i**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.2 mmol, 1.1 equiv), stirred 20 min, then Raney Ni (100 wt%) was added, pressurized with H_2 (10 bar), 24 °C, 12 h. Hydrogenolysis stage: Open reactor, $Pd(OH)_2$ (1.0 mol%) was added, pressurized with H_2 (20 bar), 50 °C, 48 h. Acid-base workup (see general procedures) and conversion into the hydrochloride salt gave **4i**·HCl; yield: 70%. The high chemical purity was confirmed by GC analysis of the free amine, >96% purity. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4i·HCl
Previously characterized.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (br, 3 H), 7.26–7.16 (m, 5 H), 3.31 (br, 1 H), 2.76 (t, *J* = 7.8 Hz, 2 H), 2.13 (m, 1 H), 1.93 (m, 1 H), 1.43 (d, *J* = 6.4 Hz, 3 H).

(*S*)-Octan-2-amine (4j)
Following general procedure D. Reductive amination stage: $Yb(OAc)_3$ (2.2 mmol, 1.1 equiv) [see pretreatment procedure at the end of general method C], anhyd MeOH (2.0 mL, 1.0 M), anhyd THF [2.0 mL, 1.0 M (used for Raney Ni transfer)], octan-2-one (**1j**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.0 mmol, 1.0 equiv), stirred for 20 min, then Raney Ni (100 wt%) was added, pressurized with H_2 (10 bar), 24 °C, 16 h. Hydrogenolysis stage: Open reactor, Pd/C (1.0 mol%) was added, pressurized with H_2 (20 bar), 50 °C, 45 h. [Note: The same result could also be obtained with $Pd(OH)_2$ (1.0 mol%), H_2 (20 bar), 50 °C, 45 h]. Acid-base workup (see general procedures), and conversion into the hydrochloride salt gave **4j**·HCl; yield: 88%. The high chemical purity was confirmed by GC analysis of the free amine, >99% purity. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4j·HCl
Previously characterized.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br s, 3 H), 3.29 (m, 1 H), 1.78 (m, 1 H), 1.70 (m, 1 H), 1.41–1.28 (m, 11 H), 0.86 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.6, 35.0, 31.6, 28.9, 25.6, 22.6, 18.8, 14.1.

(*S*)-2-Methylheptan-3-amine (4m)
Following general procedure D. Reductive amination stage: Ti(O*i*-Pr)$_4$ (6.0 mmol, 3.0 equiv), 2-methylheptan-3-one (**1m**, 2.0 mmol, 1.0 equiv), (*S*)-α-MBA (2.4 mmol, 1.2 equiv) were prestirred neat at 50 °C for 4 h. [**Note**: *this prestirring at elevated temperature was inadvertently dropped from the original experimental description*,[7] *but it is absolutely required and is consistent with our earlier description*[15] *for a similar substrate* (***3l***).] DCE (2 mL) was then added followed by a toluene (2 mL) slurry of Raney Ni (100 wt%). [Note: the DCE allows high de to be achieved, but this solvent did not allow a free-flowing slurry of Raney Ni. After our earlier literature description for **3l**, we found that a toluene slurry of Raney Ni

was excellent for transferring the Raney Ni (large-gauge needle/syringe) and importantly did not lower the de. Use of toluene as the sole reaction solvent resulted in reduced de.] Pressurized with H_2 (20 bar), 50 °C, 48 h. Hydrogenolysis stage: Open reactor, Pd/C (1.0 mol%) was added, pressurized with H_2 (20 bar), 50 °C, 45 h. Acid-base workup (see general one-pot procedure), and conversion into the hydrochloride salt gave **4m**·HCl; 88 area% chemically pure. The corresponding free amine is semi-volatile. To overcome this, the salt was added to a small separatory funnel containing aq 1 M NaOH (100 mL) and $CHCl_3$ (10 mL). The $CHCl_3$ layer was glass pipette removed and added to a column of silica gel pre-flushed with petroleum ether. The basic organic phase was once more extracted with $CHCl_3$ (5 mL) and this was also added to the silica gel column. With the free amine now on the column, petroleum ether was added and the solvent pushed down to the level of the silica gel. The polarity of the eluent was slowly raised to a final mixture of EtOAc–petroleum ether (2:3). The fractions containing the product (GC verified) were combined and aq 4.0 M HCl (~3.0 equiv) was added. This was rotary evaporated and high vacuum dried until a constant weight was achieved; yield: 76%. The high chemical purity was confirmed by GC analysis of a small portion of the free amine, >98% purity. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[7]

(*S*)-4m·HCl
Previously characterized.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br s, 3 H), 3.29 (m, 1 H), 1.78 (m, 1 H), 1.70 (m, 1 H), 1.41–1.28 (m, 11 H), 0.86 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.6, 35.0, 31.6, 28.9, 25.6, 22.6, 18.8, 14.1.

(*S*)-1,2,3,4-Tetrahydronaphthalen-1-amine (4p)
A mixture of 1-tetralone (**1p**, 0.33 mL, 2.50 mmol, 1.00 equiv), Ti(O*i*-Pr)$_4$ (0.92 mL, 3.13 mmol, 1.25 equiv), and (*S*)-α-MBA (0.35 mL, 2.75 mmol, 1.10 equiv) was prestirred (1 h) neat in the reaction vessel at 23 °C. *t*-BuOMe (5.0 mL) and Pd/C (24.0 mg, 0.23 mol%) were added, and the reaction pressurized H_2 (8.3 bar), 40 °C, 27 h. Acid-base workup (see general procedures) with rotary evaporator concentration at r.t. gave the crude product (954.0 mg, a pale yellow liquid of predominately **3p** with some **4p**) to which was added MeOH (7.0 mL), AcOH (0.90 mL, 15.20 mmol, 4.00 equiv), and Pd/C (970.0 mg, 6.0 mol%), followed by pressurization with H_2 (4.1 bar), 23 °C, 14 h. The product was filtered through celite, the celite washed with MeOH (2 × 20 mL), and aq 1.0 M HCl (5.0 mL) was added. The soln was concentrated until the nonvolatile water remained, and this was washed with Et_2O (2 × 20 mL) to remove neutral impurities. The remaining aqueous acid layer was basified with aq 2.0 M NaOH (10 mL) to pH 10–12, and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were then washed with sat. NaCl (2 × 10 mL) and dried (Na_2SO_4). After filtration, 3.0 M HCl in Et_2O (2.00 equiv) was added and the mixture was then evaporated to dryness to obtain the crude hydrochloride salt of the primary amine **4p** (747.6 mg). CH_2Cl_2 was added (0.50 M) to the salt, followed by Tf_2O (2.3 mL, 16.3 mmol, 4.00 equiv) and Et_3N (2.8 mL, 20.35 mmol, 5.00 equiv), then gently refluxed. After 40 min the mixture was quenched with sat. $NaHCO_3$ (2 × 10 mL), the CH_2Cl_2 layer was dried (Na_2SO_4), filtered, and evaporated to dryness to obtain the crude amide which was then purified by flash chromatography (heptane–EtOAc, 19:1) to give **4p** as white solid; yield: 462 mg (76% overall from **1p**); 92% ee. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[14]

(*S*)-4p·Trifluoroacetamide
R_f = 0.41 (heptane–EtOAc, 84:16).

IR (KBr): 3295, 2935, 1697, 1550, 1181 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.24 (m, 4 H), 6.56 (br s, 1 H), 5.16–5.20 (m, 1 H), 2.76–2.89 (m, 2 H), 2.07–2.13 (m, 1 H), 1.87–1.91 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 156.7, 156.4, 156.0, 138.0, 134.4, 129.6, 128.6, 128.1, 126.7, 120.3, 117.4, 114.5, 111.7, 48.5, 29.5, 29.0, 19.7.

MS (EI): *m*/*z* (%) = 243 (2), 146 (3), 130 (100), 129 (16), 115 (6), 91 (4).

Anal. Calcd for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76; Found: C, 59.29; H, 4.95; N, 5.64.

(*S*)-6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-amine (4q)
To benzosuberone (1.00 equiv, 2.50 mmol 0.37 mL) was added Ti(O*i*-Pr)$_4$ (0.92 mL, 3.13 mmol, 1.25 equiv) and (*S*)-α-MBA (0.37 mL, 2.88 mmol, 1.15 equiv). This mixture was prestirred (5 h) neat in the reaction vessel at r.t. EtOAc (5.0 mL) was added, then Pd/C (24.0 mg, 0.23 mol%; pre-activated at 60 °C/0.3 mbar, 1 h) and the reaction was pressurized with H_2 (8.3 bar) at r.t. for 36 h. Workup and hydrogenolysis stage were as for **4p** to give, after column chromatography, **4q**·trifluoroacetamide; yield: 64% (from benzosuberone); 76% ee. GC methods, product retention times, and ee determination (trifluoroacetamide GC analysis) are available.[14]

(*S*)-4q·Trifluoracetamide
R_f = 0.39 (heptane–EtOAc, 84:16).

IR (KBr): 3293, 2929, 1694, 1556, 1183 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.21 (m, 4 H), 6.62 (br s, 1 H), 5.18–5.22 (t, *J* = 8 Hz, 1 H), 2.78–2.93 (m, 2 H), 1.56–2.03 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 156.3, 155.9, 155.5, 141.2, 139.4, 130.5, 127.9, 126.6, 125.9, 120.2, 117.4, 114.5, 111.6, 54.6, 36.0, 33.2, 27.7, 27.3.

MS (EI): *m*/*z* (%) = 257 (6), 256 (10), 228 (4), 144 (100), 143 (7), 129 (34), 116 (12), 91 (7).

Anal. Calcd for $C_{13}H_{14}F_3NO$: C, 60.7; H, 5.49; N, 5.44. Found: C, 60.47; H, 5.38; N, 5.56.

Cuprate Addition for the Synthesis of Amines 3; General Procedure E
A round-bottom flask containing anhyd CuBr (3.0 equiv) was gently heated (<80 °C) by heat gun under high vacuum for 5 min, flushed with N_2, cooled to r.t., and then THF or Et_2O (30.0–35.0 mL, in total 39.0–44.0 mL, 0.10–0.08 M) was added. This soln was cooled to –45 °C and the alkylmagnesium chloride in THF (6.0 equiv) was added over 5 min. This soln was then further stirred at –45 °C for 15 min, and then cooled to –78 °C. BF_3·OEt_2 (for **3t**: 3.0 equiv; for **3u** and **3v**: 2.0 equiv) was then added over 2 min, and the soln was stirred for 5 min before the addition of a prestirred (r.t., 0.5 h) soln of the aldehyde **2** (5.0 mmol, 1.0 equiv), THF or Et_2O (7.0 mL), Ti(O*i*-Pr)$_4$ (73 μL, 0.25 mmol, 0.05 equiv), and (*S*)-α-MBA (0.68 mL, 5.25 mmol, 1.05 equiv) via cannula over 20–25 min. Additional THF or Et_2O (2.0 mL) was added to the residual imine and the resulting soln was added via cannula to the reaction flask. The reaction soln was then stirred at –78 °C for 2 h, and then at –45 °C for 1 h. The reaction was then quenched by the addition of sat. NH_4Cl–25% NH_4OH (7:3 ratio, 30 mL in total) at –45 °C for 5 min. The cooling bath was removed and stirring continued for another 90 min at r.t. Et_2O (20 mL) was added, and the biphasic soln was stirred for 5 min. The mixture was then filtered through a bed of celite and the celite subsequently washed with Et_2O (3 × 25 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with sat. NH_4Cl (2 × 25 mL), then with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and then evaporated to dryness to obtain the crude product (the de was measured at this point). Details of the synthesis of **3t**–**v** regarding GC methods, product retention times, ee determination (trifluoroacetamide GC analysis),

and the use of THF as a replacement solvent for Et_2O are available.[21]

(3*S*)-*N*-[(*S*)-1-Phenylethyl]nonan-3-amine (3t)
Following general procedure E using heptanal (0.67 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), 2.0 M EtMgCl in THF (15.0 mL, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.91 mL, 15.0 mmol, 3.0 equiv), Et_2O (44.0 mL, 0.08 M). Crude product: 81% de. Purification by flash chromatography (silica gel, hexanes–EtOAc–NH_4OH, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt; yield: 1.14 g (81%).

(*S*,*S*)-3t
Free base; R_f = 0.48 (hexanes–EtOAc–NH_4OH, 84:14:2).

IR (KBr): 3425, 3025, 2959, 2856, 1453, 1368, 1210, 1119, 1028, 700, 553 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 5 H), 3.86 (q, *J* = 6.8 Hz, 1 H), 2.29–2.23 (m, 1 H), 1.43–1.17 (m, 16 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 128.2, 126.6, 55.5, 55.0, 33.1, 31.8, 29.6, 27.1, 25.1, 24.8, 22.6, 14.1, 10.1.

MS (EI): *m*/*z* (%) = 247 (2) [M^+], 232 (7), 218 (45), 162 (58), 114 (30), 105 (100), 58 (28).

HRMS (70 eV): *m*/*z* $[M]^+$ calcd for $C_{17}H_{29}N$; 247.2300; found: 247.2293.

(5*S*)-*N*-[(*S*)-1-Phenylethyl]undecan-5-amine (3u)
Following general procedure E using heptanal (0.67 mL, 5.0 mmol, 1.00 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), 2.0 M BuMgCl in THF (15.0 mL, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), Et_2O (44.0 mL, 0.08 M). Crude product: 86% de. Purification by flash chromatography (silica gel, hexanes–EtOAc–NH_4OH, 92:6:2) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt; yield: 1.32 g (85%).

(*S*,*S*)-3u
Major product, the diastereomers were not separable via chromatography (silica gel); the mixture was characterized as the free base; R_f = 0.55 (hexanes–EtOAc–NH_4OH, 84:14:2).

IR (KBr): 3444, 3025, 2957, 2856, 1603, 1466, 1368, 1118, 909, 700, 556 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 3.86 (q, *J* = 6.4 Hz, 1 H), 2.32–2.27 (m, 1 H), 1.34–1.12 (m, 20 H), 0.90–0.82 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 128.2, 126.6, 54.9, 53.9, 34.4, 33.6, 31.8, 29.6, 27.9, 25.1, 24.8, 22.8, 22.6, 14.1, 14.0.

(*S*)-2-Methyl-*N*-[(*S*)-1-phenylethyl]octan-4-amine (3v)
Following general procedure E using 3-methylbutanal (0.54 mL, 5.0 mmol, 1.0 equiv), CuBr (2.15 g, 15.0 mmol, 3.0 equiv), 2.0 M BuMgCl in THF (15.0 mL, 30.0 mmol, 6.0 equiv), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv), Et_2O (44.0 mL, 0.08 M). Crude product: 90% de. Purification by flash chromatography (silica gel, hexanes–EtOAc–NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt; yield: 1.21 g (85%).

(*S*,*S*)-3v
Free base; R_f = 0.48 (hexanes–EtOAc–NH_4OH, 83:15:2).

IR (KBr): 3441, 3026, 2956, 2930, 2628, 1467, 1367, 1154, 1118, 700, 558 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 5 H), 3.86 (q, *J* = 6.4 Hz, 1 H), 2.38–2.32 (m, 1 H), 1.63–1.55 (m, 1 H), 1.33–1.12 (m, 12 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.84 (t, *J* = 6.8 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 128.2, 126.7, 126.6, 55.1, 52.4, 44.4, 34.8, 27.7, 24.9, 24.6, 23.5, 22.8, 22.6, 14.0.

MS (EI): *m*/*z* (%) = 247 (2) [M^+], 232 (4), 190 (100), 106 (10), 105 (82), 86 (48).

HRMS (70 eV): *m*/*z* [M^+] calcd for $C_{17}H_{29}N$: 247.2300; found: 247.2295.

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(2) We have demonstrated this for primary amines **4p** and **4q**, i.e., Pd/C (6.0 mol%), AcOH, low hydrogen pressures (4 bar), r.t., allowed hydrogenolysis; see the procedure for **4p** (experimental section) for an example. Note that the racemization of chiral amines is possible in the presence of Pd, see ref. 3.

(3) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.–Eur. J.* **2007**, *13*, 2034.

(4) For supportive examples, see: (a) Nugent, T. C.; Seemayer, R. *Org. Process Res. Dev.* **2006**, *10*, 142. (b) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527. (c) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079. (d) Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138.

(5) For the reductive amination of keto esters, see: Nugent, T. C.; Ghosh, A. *Eur. J. Org. Chem.* **2007**, 3863.

(6) See the following reference which strongly implies that chloro-, bromo-, and presumably iodoaromatic moieties would be hydrogenolyzed when using our methods: Bringmann, G.; Geisler, J.-P.; Geuder, T.; Künkel, G.; Kinzinger, L. *Liebigs Ann. Chem.* **1990**, 795.

(7) Nugent, T. C.; Negru, D. E.; El-Shazly, M.; Hu, D.; Sadiq, A.; Bibi, A.; Umar, M. N. *Adv. Synth. Catal.* **2011**, *353*, 2085; and supporting information therein.

(8) See ref. 7, p 2087 for the text discussion of compound **2a**.

(9) See ref. 7, compounds **2d** and **3d** (Tables 1 and 2).

(10) See ref. 6, p 797, in reference to aromatic halide removal: 'This well-known hydro-dehalogenation can be prevented only by application of a special catalyst mixture Rh_2O_3/PtO_2 (3:2), which thus allows the preparation of the corresponding secondary amine **9m** with a still significant stereoselectivity (see Table 1).'

(11) Process for the preparation of (*S*,*S*)-*cis*-2-benzhydryl-3-benzylaminoquinuclidine: Nugent, T. C.; Seemayer, R. WO 2004035575, **2004**.

(12) See refs. 7 and 4a for examples of success using crystallization to impart high de, in particular in the supporting information of those references.
(13) From greater than 20 examples, one substrate remains an oddity regarding the inconsistency of its stereoselectivity, in particular **3o** (see Figure 4). We have previously reported its de as 94%, see ref. 14, but more recent unpublished research results of ours have shown that the de, and consequently the ee for this substrate, actually ranges between 84–94% de (average = 89% de). It is difficult to speculate on the source of the problem because other alkyl aryl ketones, e.g. *o*-substituted acetophenones, required the same reaction conditions or slightly harsher (albeit using a different solvent), and show no discrepancies in stereoselectivity. Racemization events can occur in the presence of Pd/C at high temperatures, e.g., see ref. 3.
(14) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289; and supporting information therein.
(15) Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K.; Mohanty, R. R. *Org. Lett.* **2005**, *7*, 4967; and supporting information therein.
(16) The experimental description, ref. 7, for compounds **3m** and **4m** lacked an important detail, i.e., prestirring of the reagents and starting materials neat at elevated temperature (50 °C, 4 h) before pressurization with H_2. See the experimental section provided here for the procedures for **3m** and **4m** for further details.
(17) Reeves, J. T.; Tan, Z.; Han, Z. S.; Li, G.; Zhang, Y.; Xu, Y.; Reeves, D. C.; Gonnella, N. C.; Ma, S.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1400.
(18) Nugent, T. C.; El-Shazly, M.; Wakchaure, V. N. *J. Org. Chem.* **2008**, *73*, 1297.
(19) See ref. 18, p 1302, the text and footnote 34, for specific examples.
(20) We cannot rule out the possibility that a one-pot reductive amination–hydrogenolysis has been previously achieved, but our attempts to use key word and phrase searches failed to identify anything regarding this topic in the literature. To see our research in this area, see ref. 7.
(21) Wakchaure, V. N.; Mohanty, R. R.; Shaikh, A. J.; Nugent, T. C. *Eur. J. Org. Chem.* **2007**, 959.
(22) Here our educated guess is that **3v** would be produced in ~85% de using reductive amination with the appropriate ketone precursor.
(23) (a) Nugent, T. C.; Umar, M. N.; Bibi, A. *Org. Biomol. Chem.* **2010**, *8*, 4085. (b) Nugent, T. C.; Bibi, A.; Sadiq, A.; Shoaib, M.; Umar, M. N.; Tehrani, F. N. *Org. Biomol. Chem.* **2012**, *10*, 9287.

