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

ARTICLE *in* ADVANCED SYNTHESIS & CATALYSIS · JANUARY 2012

Impact Factor: 5.66 · DOI: 10.1002/adsc.201100250

DOI: 10.1002/adsc.201100250

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

Thomas C. Nugent,[a,*] Daniela E. Negru,[a] Mohamed El-Shazly,[a] Dan Hu,[a] Abdul Sadiq,[a] Ahtaram Bibi,[a] and M. Naveed Umar[a]

[a] Department of Chemistry, School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, 28759 Bremen, Germany
Fax: (+49)-421-200-3229; e-mail: t.nugent@jacobs-university.de

Received: April 3, 2011; Published online: August 4, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100250.

Abstract: Difficult-to-access chiral primary amines were formed in good to high yield and *ee* using a rare example of a one-pot synthesis from prochiral ketones (sequential reductive amination-hydrogenloysis). As a highlight we also demonstrate a one-pot reductive amination-hydrogenolysis-reductive amination (five reactions) of *ortho*-methoxyacetophenone resulting in the chiral diamine 1-(2-methoxyphenyl)ethyl-(2-pyridylmethyl)-amine (**4**) (58% overall yield, >99% *ee*), a new organocatalyst for aqueous enantioselective aldol reactions.

Keywords: asymmetric reductive amination; chiral amines; hydrogenolysis; primary amine synthesis

Introduction

Suppression of disease pathways entails the use of medical agents with pinpoint structural features conferred through the functional group diversification of promising preclinical templates. Within this framework, chiral amines often play an integral role in the drug discovery process because they can provide a high density of structural information, i.e., their handedness coupled with their strong propensity for hydrogen bond formation at a relevant biological binding site.

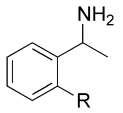
Chiral amine-based pharmaceutical drugs and alkaloid natural products overwhelmingly contain secondary or tertiary amines, and, to a lesser degree, the corresponding amides with functionalized side chains. Unfortunately current methods do not allow the introduction of nitrogen, in those forms, into advanced intermediates *via* operationally simple, stepwise efficient (one-step), enantioselective catalytic methods. Consequently, chiral *primary amines* are frequently the reliable building blocks that chemists turn to during the synthetic planning of a final target, while medicinal chemists seek them out because they hold greater diversification potential *vs.* secondary or tertiary chiral amine building blocks.

Fifteen years ago chiral amine synthesis (non-amino acid) was characterized by individual solutions, today it holds the elevated stature of a standalone field represented by a diverse number of reliable methods.[1,2] Nonetheless, reaction step efficiency has yet to be broadly addressed. Exceptions are reports by Kadyrov (chemical),[3] Kroutil (enzymatic),[4] and Bornscheuer (enzymatic)[5] who have demonstrated efficient one-pot syntheses of chiral primary amines from prochiral ketones. These methods rely on reductive amination and this approach continues to be underappreciated for the synthesis of chiral amines.[6]

Herein, we introduce a rare example of a one-pot chemical synthesis of chiral primary amines from prochiral aryl alkyl or alkyl alkyl′ ketones, exploiting an asymmetric reductive amination-hydrogenolysis sequence. Furthermore, four of the primary amine products synthesized here (**3b–e**) are documented as difficult to access,[7] and none of these sterically congested chiral amines were reported using the above noted one-pot methods.[3–5]

Results and Discussion

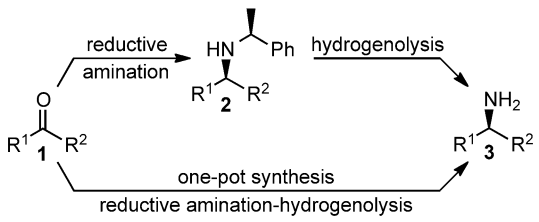
The literature is replete with examples of the shortcomings associated with chiral primary amine synthesis, among them, multistep syntheses (>2 steps), harsh nitrogen deprotection conditions, and/or low overall yield are common.[8] Chiral amine syntheses



Scheme 1. Generic *ortho*-substituted phenylethylamines.

from acetophenone or its *para*- and *meta*-substituted analogues are no exceptions, but the corresponding primary amines are nonetheless accessible and commonly reported on. By contrast the *ortho*-substituted variants (Scheme 1) are well documented as cumbersome to obtain.[7a] For example, the resolution of racemic *ortho*-substituted phenylethylamines can provide high *ee*, but in low overall yield.[9] The use of chiral amine auxiliaries has been reported, but this approach generally lacks reaction step efficiency. For example, the phenylethylamine (PEA) auxiliary has been employed *via* the corresponding chiral imines of *ortho*-substituted acetophenones,[10] while the *tert*-butylsulfinamide auxiliary has been taken advantage of *via* formal carbanion addition to *N*-sulfinylaldimines of *ortho*-substituted benzaldehydes.[11] When the employed method shifts to the enantioselective hydrogenation of *ortho*-substituted arylenamides, only three research groups have made a point of studying more than one substrate example.[12,13,14] Of those, remarkable enantioselectivities have been achieved by Zhang,[7a] however three distinct reaction steps are still required to access the primary amine. The enantioselective reduction of *N*-arylimines is currently popular,[15] and Xiao's two-step (reductive amination) method stands out regarding overall brevity, yield, and enantioselectivity.[15b] Finally, other methods for *ortho*-substituted phenylethylamine synthesis are known but less frequently reported on,[16] of these Zhang's two-step method entails the enantioselective reduction of unactivated imines which could be considered as forward looking.[16a]

In the context of reaction step efficiency, we speculated whether it would be possible to perform a reductive amination using a heterogeneous hydrogenation catalyst in the presence of (*R*)- or (*S*)-phenylethylamine (PEA), and, in a best case scenario, simply raise the temperature to effect a hydrogenolysis of the auxiliary (Scheme 2) in a one-pot sequence.



Scheme 2. Two-step *vs.* one-pot approach to chiral primary amine synthesis.

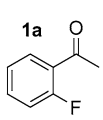
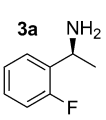
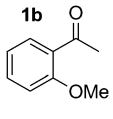
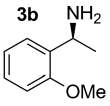
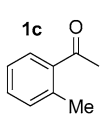
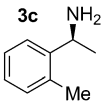
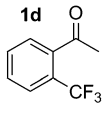
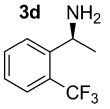
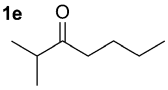
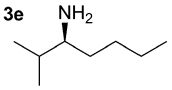
To the best of our knowledge there are no examples of this sequential reaction in the chiral amine literature and our own previous attempts failed.[17] Here we show that it is not only possible and generic in nature, but also grants access to chiral amine structures whose synthetic histories are punctuated by a lack of accomplishment.

We have previously synthesized enantioenriched primary amines *via* two-step processes originating from the corresponding ketones (Scheme 2)[7b,17,18] or aldehydes (not shown),[19] but not from demanding *ortho*-substituted acetophenones and not in a one-pot process. To explore this possibility we first reductively aminated these sterically hindered ketones with (*S*)-phenylethylamine, (*S*)-PEA, in the presence of a heterogeneous hydrogenation catalyst under pressurized hydrogen, and isolated the secondary amine products (*S*,*S*)-**2** (major) and (*S*,*R*)-**2** (minor), Table 1.

Solvent screening experiments showed *i*-PrOAc to be universal and optimal regarding reaction rate, diastereoselectivity, and by-product suppression, while MeOH, EtOH, EtOAc, $PhCH_3$, CH_2Cl_2, and 1,2-dichloroethane were inferior. An exception was noted when examining a sterically challenging alkyl alkyl′ ketone, 2-methyl-3-heptanone (Table 1, entry 7), here a 1,2-dichloroethane/toluene solvent mixture proved more effective.[20] In contrast to the solvent, the optimal heterogenous hydrogenation catalyst was strongly dependent on the *ortho*-substituted acetophenone being examined. For example, Raney-Ni provided the highest diastereoselectivity and fully consumed the *ortho*-fluoro and *ortho*-methoxy substrates (Table 1, entries 1 and 3), however, e.g., the *ortho*-methyl substrate (entry 4) was not completely consumed even after extended reaction times (72 h) with the Raney-Ni catalyst. For the *ortho*-methyl (entry 4) and *ortho*-trifluoromethyl substrates (entry 6), Pd/Al_2O_3 (1.5 mol%) was the most useful reductive amination catalyst. These catalysts were identified after screening the following commercially available hydrogenation catalysts: Raney-nickel, Pt/C, Pd/C, Pd/Al_2O_3, $Pd/CaCO_3$, and $Pd(OH)_2$.

For all crude secondary amine products (**2**), we were able to define crystallization procedures allowing high diastereoenrichment with repeatable yields [Table 1, see *de* (enriched)]. For those originating from *ortho*-substituted aromatic ketones, (**2a**–**d**), crystallization of the crude product with phthalic acid (1:1 salt) from mixtures of *i*-PrOH/heptane or simply *i*-PrOH was optimal (see Table 1 and Supporting Information). For the sterically congested aliphatic amine **2e**, crystallization of the HCl salt from cyclohexane was required. In this way, we successfully circumvented the need for chromatography, allowing simple multi-gram preparations of compounds **2** in diastereopure form.

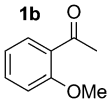
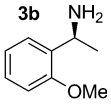
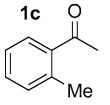
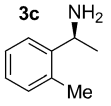
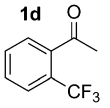
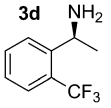
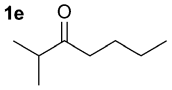
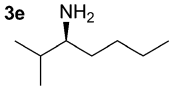
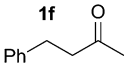
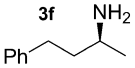
Table 1. Two-step primary amine synthesis from ketones.

Entry	Ketone **1**	Reductive amination prod. **2a–e**[a]				Hydrogenolysis prod. **3a–e**[b]		
		Catalyst[c]	*de* (crude)[d]	*de* (enriched)[e]	Yield (from **1**)[e]		*ee*	Yield[f] (from **2**)
1		Raney-Ni 100 wt%	97	98[g,h]	79[g,h]		98	78
2		Pt/C 0.5 mol%	40	99	56			
3		Raney-Ni 100 wt%	98	98[g,i]	97[g,i]		98	95
4		Pd/Al_2O_3 1.5 mol%	74	95	67		97	87
5			NA	>99[j]	48[j]			
6		Pd/Al_2O_3 1.5 mol%	88	>99	66		98	90
7		Raney-Ni 100 wt%	89	97[f]	64		97	84

[a] *Secondary amine:* in general, ketone (2–3 mmol), PEA (1.2 equiv.), *i*-PrOAc (0.5 M), $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 or 1.60 equiv.), H_2 (10, 15, or 20 bar), at 23 °C (**1c** at 35 °C and **1e** at 50 °C), 24 h (see Supporting Information).
[b] *Primary amine:* secondary amine **2** (2–3 mmol), MeOH (0.5 M), Pd/C (0.50 mol%), H_2 (15 or 20 bar), at 50, 55, or 60 °C, 24 h.
[c] Based on the limiting reagent (ketone).
[d] After work-up (GC analysis).
[e] After crystallization with phthalic acid (see Supporting Information).
[f] Isolated as the HCl salt.
[g] No crystallization performed.
[h] Column chromatography performed.
[i] Chemically pure after work-up.
[j] A second crystallization was performed, the yield is based on ketone **1c** (entry 5).

The noted crystallization approach initially failed when examining the purification of secondary amine **2a** (Table 1, entry 1). Reductive amination of *o*-fluoroacetophenone, using Raney-Ni, enabled high *de* (98%), but also gave the previously described defluorination by-product (6–10%),[10i] which could be readily removed using flash chromatography (Table 1, entry 1, 79% yield, 98% *de*), but not by crystallization. To ameliorate this problem we reductively aminated *o*-fluoroacetophenone using Pt/C (0.5 mol%), shutting down the defluorination pathway but grossly and negatively impacting the *de* (40%) of **2a**. In a rare example of highly efficient crystallization, this low *de* product (70:30 *dr*) was reliably enriched to 99% *de* in 55–60% yield, from ketone **1a**, after a single crystallization (Table 1, entry 2). For the remaining products (**2**, Table 1), the crude *de* was sufficiently high to readily allow enrichment to ≥97% *de* after a single crystallization, albeit **2c**, which has a mediocre *de* (74% crude), required a second crystallization (Table 1, compare entries 4 and 5). Thus depending on the intended scale of the reaction, we have provided small- and large-scale isolation solutions. Finally, in a second step, we obtained all of the primary amines (**3a–e**) in ≥97% *ee* with good to excellent yield after hydrogenolysis (50–60 °C) of the diastereoenriched secondary amines **2a–e** in MeOH (Table 1).

Table 2. One-pot sequential reductive amination-hydrogenolysis.

Entry	Starting ketone (**1**)	Primary amine product (**3**)	Primary amine data[a]	
			ee [%]	Yield [%][b]
1			96	72
2			71	70
3			90	60
4			89	76[c]
5[d]			85	70
6[d]			82	88

[a] *Reductive amination stage:* see Table 1 and Supporting Information; *hydrogenolysis stage:* Pd/C or $Pd(OH)_2$ (1.0 mol%), H_2 (20 bar), 50 or 55 °C, 48 h. $Pd(OH)_2$ was used for entries 2, 3, and 5.

[b] Isolated as the HCl salt in >95% chemical purity after acid-base work-up, see Supporting Information.

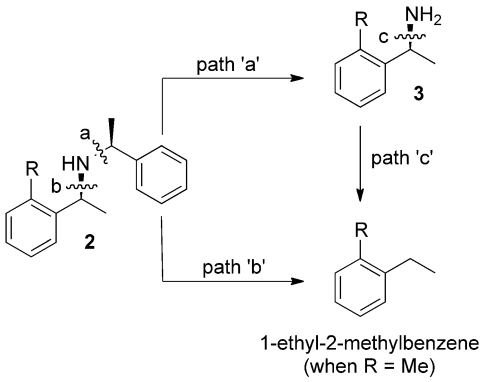
[c] Column chromatography performed,[21] see Supporting Information.

[d] *Reductive amination stage* used: PEA (1.2 equiv.), $Yb(OAc)_3$ (1.1 equiv.), MeOH/THF (1:1, 0.5 M), Raney-Ni (100 wt%), H_2 (10 bar), 24 °C, 12 or 16 h; *hydrogenolysis stage:* as in footnote[a] of Table 1.

To achieve a one-pot reaction, we reductively aminated the ketones (**1**) under very similar reaction conditions as those found in Table 1, except now, without work-up or solvent exchange, we added Pd/C or $Pd(OH)_2$/C (1.0 mol%) allowing *in situ* hydrogenolysis of the secondary amines (**2**) into primary amines (**3**) (Table 2). The success of this one-pot procedure is clear based on the overall yields alone, but the hydrogenolysis stage did require approximately double the reaction time as compared to the hydrogenolysis of pure **2** using Pd/C (0.50 mol%) in MeOH (Table 1). Hydrogenolysis rate depressing factors, for the one-pot method, can most likely be linked to: (i) the non-alcoholic reaction solvents, (ii) in some instances the slightly lower employed reaction temperatures, and (iii) the heterogeneous reaction mixture, inherited from the reductive amination stage, may reduce (*via* physical impediment and/or promotion of conglomeration) the available Pd surface for hydrogenolysis. Regarding the last point, the spent heterogeneous reductive amination catalyst and the presence of finely divided and suspended TiO_2, from the *in situ* hydrolyzed $Ti(O\text{-}i\text{-}Pr)_4$, are likely culprits.

Concerning the isolation of the primary amine products **3b–g** (Table 2), all were obtained in high chemical purity (>95%, GC and ^1H NMR, see Supporting Information) as their HCl salts, in good yield, after acid-base work-up procedures;[21] but their *ee*s were lower, reflecting the native *de*s of the corresponding secondary amines **2** before crystallization (compare *ee*s of **3** in Table 2 with the "crude *de*s" of secondary amines **2** in Table 1).

Our optimization of the one-pot procedure (Table 2) showed that close adherence to the indicated hydrogenolysis reaction times was vital for repeatable yields to be obtained.[22] For example, the primary amine products **3**, arrived at from aryl methyl ketones **1a–d**, are susceptible to yield reduction *via* two non-productive hydrogenolysis pathways (Scheme 3, path 'b' and 'c'). Although path 'b' is rarely observed, path 'c' is a concern, but its influence

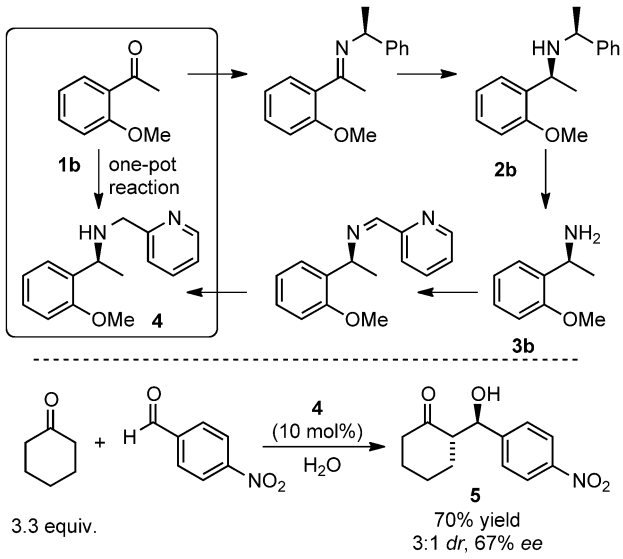


Scheme 3. Hydrogenolysis by-product pathways.

on the yield of the desired product can often be suppressed by careful attention to temperature and time parameters.

To determine which of these non-productive pathways was operative for our substrates, we looked for 1-ethyl-2-methylbenzene (Scheme 3, R = Me) when converting pure **2c** into **3c** (Table 1 reaction conditions); and confirmed its presence based on its coelution with an authentic sample (GC). The chromatogram further revealed that 1-ethyl-2-methylbenzene had formed *via* pathway 'a' followed by 'c'. This was unmistakable because of the complete lack of phenylethylamine, a unique by-product of pathway 'b' in the same chromatogram.[23] These follow-up studies confirmed our earlier experimental observations that extended hydrogenolysis reaction times are detrimental to the yield of **3** and confirmed our suspicion that deamination of **3** was indeed occurring. Although the non-benzylic amines **3e–f** (Table 2) are not vulnerable to these benzylic carbon-nitrogen degradation pathways, they are nonetheless susceptible to racemization events at high temperature over prolonged reaction times.[24]

Finally, to push the limits of the developed method, we subjected ketone **1b** to a one-pot reductive amination-hydrogenolysis-reductive amination sequence, five reactions in total, forming diamine **4** in 58% yield (from **1b**) in >99% *ee* (Scheme 4, *top*). In this sequence, the second reductive amination consumed 2-pyridinecarboxaldehyde, which was added after primary amine **3b** had fully accumulated (GC analysis). This second carbonyl partner was chosen for two reasons, one to show that a diverse aldehyde could be used, but more importantly to gain access to analogues of pyridine-based chiral diamines which have recently been reported as good organocatalysts for aqueous aldol reactions.[25] Use of diamine **4**, with a 2,4-dinitrobenzenesulfonic acid (10 mol%) cocatalyst, indeed catalyzed the aldol reaction (Scheme 4, *bottom*, 60 h at 45 °C), setting a possible foundation for future investigations of enantioselective aqueous aldol reactions. Finally, the one-pot reductive amination-hydrogenolysis-reductive amination sequence could be extended to the use of unsymmetrical ketones, as the carbonyl component, for the second reductive amination, but in our hands poor diastereoselectivity was always noted and this avenue was not further pursued.



Scheme 4. One-pot synthesis of an aldol organocatalyst.

Conclusions

In closing, a one-pot method enabling chromatography-free isolation of challenging chiral primary amines has been demonstrated with very good yield (60–88%), especially when noting that three sequential reactions have taken place (imine formation, imine reduction, and hydrogenolysis of the auxiliary). The final *ee*s range from excellent (96%) to mediocre (71%) and reflect the *de* of the *in situ* formed secondary amine products (Table 2). By contrast, across-the-board high *ee*s (97–98%) can be achieved for the primary amines using a two-step method (Table 1) with good overall yields and again without the need for chromatography. Finally, the method has been extended to a reductive amination-hydrogenolysis-reductive amination, providing diamine **4** which serves as an organocatalyst for aqueous aldol reactions.

Experimental Section

General Synthesis of Secondary Amines 2 (Reductive Amination)

In a reaction vessel under nitrogen containing *i*-PrOAc (2.0 mL) were combined the *ortho*-substituted acetophenone **1** (2.0 mmol, 1.0 equiv.), (*S*)-α-methylbenzylamine (1.2 equiv.) and $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 equiv.). This mixture was stirred for 30 min and then an *i*-PrOAc (2.0 mL) slurry of Raney-Ni [100 wt% based on the ketone, triturated first with EtOH (3×2 mL) and then with *i*-PrOAc (3×2 mL)] was added or in the case of Pd- or Pt-based catalysts, the solid heterogeneous catalyst was simply added followed by further addition of *i*-PrOAc (2.0 mL). [Note: 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 at 10–20 bar H_2 at 24 or 35 °C (50 °C for **1e**), depending on the specific substrate, with stirring. After 24 h (<4 area% of the ketone substrate and imine intermediate remained, GC analysis), the reaction mixture was diluted with EtOAc (30 mL) and vigorously stirred with aqueous NaOH (1.0 M, 30 mL) for 4 h. The heterogeneous biphasic mixture was then filtered through a bed of celite and the celite subse-

quently washed with EtOAc (3×10 mL). The aqueous layer was further extracted with EtOAc (3×20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated (rotary evaporator). The crude product was then dried under high vacuum until a constant weight was achieved (usually overnight). Variations from this general procedure are described in the specific examples, see Supporting Information.

General Synthesis of Enantioenriched Primary Amines (3a–e) from Secondary Amines (2a–e)

The secondary amines **2** (Table 1) were hydrogenolyzed in MeOH (0.5 M) using Pd/C (0.5 mol%), at 50–60 °C, under 15 or 20 bar H_2, over 24 h. Work-up: at room temperature the reaction was diluted with MeOH (50 mL), and aqueous HCl (37%, 3.0 equiv.) was added. This solution was filtered through celite and the celite subsequently rinsed with MeOH. The filtrate was evaporated resulting in a solid residue (HCl salt of primary amine). A small amount of the HCl salt was converted into the free amine and a GC was recorded. If there was one GC peak representing the product (all other peaks, in total, <4 area%), the ^1H and ^{13}C NMR spectra of the HCl salt were recorded. If the chromatogram showed >4 area% impurities, the following procedure was used. The HCl salt of the primary amine was added to a mixture of $CHCl_3$ (50 mL) and distilled water (50 mL). [Note: It is important to use $CHCl_3$ here and not CH_2Cl_2.] The $CHCl_3$ layer was further extracted with water (2×15 mL), and the combined water extracts then had CH_2Cl_2 (30 mL) added. To this biphasic solution was added NaOH (4.0 M) until the aqueous layer was strongly basic (> 11 pH). The CH_2Cl_2 extract was then removed, and the basic water layer was further extracted (CH_2Cl_2, 3×30 mL). To the combined CH_2Cl_2 extracts was added aqueous HCl (37%, 3.0 equiv.). Concentration (rotary evaporator, bath temperature initial: 30 °C; final: ~70 °C) provided an off white solid that was then dried under high vacuum until a constant weight was achieved (usually overnight). This method reliably allowed all of the primary amines (**3**) to be isolated in high chemical purity (>96% by GC). Variations from this general procedure are described in the Supporting Informatiion. [Note: All of the free primary amines (**3**) in this manuscript, unlike their phthalic acid or HCl salts, should be considered as being volatile under rotary evaporation.]

General One-Pot Synthesis of Enantioenriched Primary Amines (3b–g) from Ketones (1b–g)

In a reaction vessel under nitrogen, $Yb(OAc)_3$ (2.2 mmol, 1.1 equiv.) [dried at 80 °C under high vacuum until a constant weight was achieved (generally 12 h)] or $Ti(O\text{-}i\text{-}Pr)_4$ (2.4 mmol, 1.2 equiv.) was added, followed by the solvent (2.0 mL, 1.0 M), ketone **1b–1g** (2.0 mmol, 1.0 equiv.), and (*S*)-α-methylbenzylamine (2.4 mmol, 1.2 equiv.). This mixture was stirred for 30 min, at room temperature, 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, an additional 2.0 mL of reaction solvent was added. [Note: 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 at 10–20 bar H_2 at 24 or 35 °C (50 °C for **1e**), depending on the specific substrate, with stirring. After stirring for 12–48 h, <4 area% of the ketone substrate and imine intermediate (combined) remained, GC analysis, and Pd/C (1.0 mol%) or $Pd(OH)_2$ (1.0 mol%) was added. The reaction mixture was then heated at 50 or 55 °C under 20 bar H_2. Importantly, the reaction is worked-up when 5–6 area% of the secondary amine still remains, which is most often at 48 h. Work-up: the mixture was diluted with EtOAc (40 mL) and aqueous NaOH (1.0 M, 30 mL) added. After vigorous stirring for 4 h in a capped Erlenmeyer flask, the heterogeneous two phase solution 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 more than required.] The aqueous layer was further extracted with EtOAc (3×20 mL), and the combined organic layers were then treated with concentrated HCl (37% aqueous, 3 equiv.). This mixture 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 distilled H_2O (50 mL) and $CHCl_3$ (50 mL) were added. [Note: It is important to use $CHCl_3$ here and not CH_2Cl_2.] The $CHCl_3$ layer was further extracted with distilled H_2O (2×10 mL). To the combined water layers, CH_2Cl_2 (50 mL) was added, and then the aqueous phase was made strongly basic (pH>11) with NaOH (4.0 M). After removal of the CH_2Cl_2 layer, the basic water layer was further extracted with CH_2Cl_2 (2×30 mL). To the combined CH_2Cl_2 layers was added HCl (37% aqueous, 3 equiv.) and this was concentrated (rotary evaporator, bath temperature initial: 30 °C; ending: ~70 °C) providing an off white solid that was then dried under high vacuum until a constant weight was achieved (usually overnight). Variations from this general procedure are found in the Supporting Information. [Note: All of the free primary amines (**3**) in this manuscript, unlike their phthalic acid or HCl salts, should be considered as being volatile under rotary evaporation.]

Acknowledgements

*We are grateful for financial support from Jacobs University Bremen and the HEC of Pakistan. We also thank Mohammad Shoaib for identifying cyclohexane as a good solvent for the crystallization of **2e**. This work has been performed within the graduate program of Nanomolecular Science.*

References

[1] For recent reviews, see: a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; b) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740; c) N. Fleury-Brégeot, V. de La Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346–1371; d) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819; e) F. Collet, R. H. Dodd, P.

Dauban, *Chem. Commun.* **2009**, *34*, 5061–5074; f) R. L. Patman, J. F. Bower, I. S. Kim, M. J. Krische, *Aldrichimica Acta* **2008**, *41*, 95–104; g) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339.

[2] For recent books on the subject and book chapters, see: a) *Chiral Amine Synthesis. Methods, Developments and Applications*, (Ed.: T. C. Nugent), Wiley-VCH: Weinheim, **2010**; b) R. Dorta, *Iridium-catalyzed hydroamination*, in: *Iridium Complexes in Organic Synthesis*, (Eds.: L. A. Oro, C. Claver), Wiley-VCH, Weinheim, **2009**, pp 145–172; c) C. Claver, E. Fernández, *Imine hydrogenation*, in: *Modern Reduction Methods*, (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**, pp 237–269; d) M. Wills, *Imino Reductions by Transfer Hydrogenation*, in: *Modern Reduction Methods*, (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**, pp 271–296.

[3] R. Kadyrov, T. H. Riermeier, *Angew. Chem.* **2003**, *115*, 5630–5632; *Angew. Chem. Int. Ed.* **2003**, *42*, 5472–5474.

[4] D. Koszelewski, I. Lavandera, D. Clay, G. M. Guebitz, D. Rozzell, W. Kroutil, *Angew. Chem.* **2008**, *120*, 9477–9480; *Angew. Chem. Int. Ed.* **2008**, *47*, 9337–9340.

[5] M. Höhne, S. Kühl, K. Robins, U. T. Bornscheuer, *ChemBioChem* **2008**, *9*, 363–365.

[6] For recent examples of advances in reductive amination, see: a) C. Wang, A. Pettman, J. Basca, J. Xiao, *Angew. Chem.* **2010**, *122*, 7710–7714; *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552; b) A. Kumar, S. Sharma, R. A. Maurya, *Adv. Synth. Catal.* **2010**, *352*, 2227- 2232.

[7] a) W. Zhang, X. Zhang, *Angew. Chem.* **2006**, *118*, 5641–5644; *Angew. Chem. Int. Ed.* **2006**, *45*, 5515–5518; b) T. C. Nugent, V. N. Wakchaure, A. K. Ghosh, R. R. Mohanty, *Org. Lett.* **2005**, *7*, 4967–4970.

[8] For an example that starts to address some of these concerns, see: D. J. Wallace, K. R. Campos, C. S. Shultz, A. Klapars, D. Zewge, B. R. Crump, B. D. Phenix, J. C. McWilliams, S. Krska, Y. Sun, C.-y. Chen, F. Spindler, *Org. Process Res. Dev.* **2009**, *13*, 84–90.

[9] a) L. M. Klingensmith, K. A. Nadeau, G. A. Moniz, *Tetrahedron Lett.* **2007**, *48*, 4589–4593; b) T. Shimada, Y. Kobayashi, K. Saigo, *Tetrahedron: Asymmetry* **2005**, *16*, 3807–3813; c) D. T. Chapman, D. H. G. Crout, M. Mahmoudian, D. I. C. Scopes, P. W. Smith, *Chem. Commun.* **1996**, *10*, 2415–2416.

[10] a) J. Müslehiddinoğlu, J. Li, S. Tummala, R. Deshpande, *Org. Process Res. Dev.* **2010**, *14*, 890–894; b) D. Polet, A. Alexakis, *Org. Lett.* **2005**, *7*, 1621–1624; c) E. P. Kündig, C. Botuha, G. Lemercier, P. Romanens, L. Saudan, S. Thibault, *Helv. Chim. Acta* **2004**, *87*, 561–579; d) M. Kanai, M. Yasumoto, Y. Kuriyama, K. Inomiya, Y. Katsuhara, K. Higashiyama, A. Ishii, *Org. Lett.* **2003**, *5*, 1007–1010; e) M. Tiecco, L. Testaferri, C. Santi, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, *Tetrahedron: Asymmetry* **2000**, *11*, 4645–4650; f) C. Cimarelli, G. Palmieri, *Tetrahedron: Asymmetry* **2000**, *11*, 2555–2563; g) G. Bringmann, J.-P. Geisler, *J. Fluorine Chem.* **1990**, *49*, 67–73; h) E. Juaristi, J. L. León-Romo, A. Reyes, J. Escalante, *Tetrahedron: Asymmetry* **1999**, *10*, 2441–2495; i) G. Bringmann, J.-P. Geisler, T. Geuder, G. Künkel, L. Kinzinger, *Liebigs Ann. Chem.* **1990**, *8*, 795–805; j) M. B. Eleveld, H. Hogeveen, *Tetrahedron Lett.* **1984**, *25*, 5187–5190.

[11] a) K. Brak, J. A. Ellman, *J. Am. Chem. Soc.* **2009**, *131*, 3850–3851; b) X.-W. Sun, M. Liu, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2008**, *10*, 1259–1262.

[12] For reports examining multiple *ortho*-substituted arylenamide substrates, see ref.[7a] and a) T. Imamoto, T. Itoh, K. Yoshida, I. D. Gridnev, *Chem. Asian J.* **2008**, *3*, 1636–1641; b) I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276; c) M. J. Burk, Y. M. Wang, J. R. Lee, *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143.

[13] For recent literature examples detailing only one *ortho*-substituted arylenamide substrate (*ortho*-F excluded, see ref.[14]), see the following and literature cited therein: a) G. Li, J. C. Antilla, *Org. Lett.* **2009**, *11*, 1075–1078; b) G. Erre, S. Enthaler, K. Junge, D. Addis, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 1437–1441; c) Y. Fu, X.-X. Guo, S.-F. Zhu, A.-G. Hu, J.-H. Xie, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648–4655; d) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355–2361.

[14] *ortho*-Fluorophenylenamide is the most popular *ortho*-substituted arylenamide to be examined, yet it is not representative of the much greater difficulties encountered when reducing all other *ortho*-substituted enamide substrates (see refs.[12,13]). The similar size of fluorine, relative to hydrogen, is likely the reason why success has been reported by multiple groups, see ref.[12c], and the following references and literature cited therein: a) C.-J. Wang, F. Gao, G. Liang, *Org. Lett.* **2008**, *10*, 4711–4714; b) S. P. Allwein, J. C. McWilliams, E. A. Secord, D. R. Mowrey, T. D. Nelson, M. H. Kress, *Tetrahedron Lett.* **2006**, *47*, 6409–6412; c) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2002**, *114*, 2454–2456; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348–2350.

[15] a) S. Zhou, S. Fleischer, K. Junge, S. Das, D. Addis, M. Beller, *Angew. Chem.* **2010**, *122*, 8298-8302; *Angew. Chem. Int. Ed.* **2010**, *49*, 8121–8125; b) C. Li, B. Villa-Marcos J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969; c) A. V. Malkov, S. Stončius, P. Kočovský, *Angew. Chem.* **2007**, *119*, 3796–3798; *Angew. Chem. Int. Ed.* **2007**, *46*, 3722–3724; d) M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089–3092; e) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783; f) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736–7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567; g) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590–7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; h) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827; i) M. C. Hansen, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 713–715.

[16] a) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883; b) C. Wang, X. Wu, L. Zhou, J. Sun, *Chem. Eur. J.* **2008**, *14*, 8789–8792; c) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729–3734.

[17] T. C. Nugent, A. K. Ghosh, V. N. Wakchaure, R. R. Mohanty, *Adv. Synth. Catal.* **2006**, *348*, 1289–1299.

[18] T. C. Nugent, M. El-Shazly, V. N. Wakchaure, *J. Org. Chem.* **2008**, *73*, 1297–1305.
[19] V. N. Wakchaure, R. R. Mohanty, A. J. Shaikh, T. C. Nugent, *Eur. J. Org. Chem.* **2007**, 959–964.
[20] 1,2-Dichloroethane is the optimal reaction solvent, but transfer of the Raney-Ni slurry into the reaction with this solvent (*via* a wide gauge needle and syringe) was not feasible due to the technical problem that 1,2-dichloroethane slurries of Raney-Ni were not free-flowing. This was overcome by using a toluene slurry (see the Supporting Information). Fortunately, the toluene did not adversely affect the positive attributes of 1,2-dichloroethane solvent.
[21] The aliphatic primary amine **3e** was of lower chemical purity, 88 area% (GC), after work-up. It was consequently chromatographed before the yield was calculated. All primary amines (**3**) are semi-volatile to volatile, see the Supporting Information for the method of careful chromatography of **3e**.
[22] The hydrogenolysis reactions performed in Table 1 also had to be closely monitored, extended reaction times reduced the yield.
[23] It is possible that phenylethylamine formed but underwent rapid hydrogenolysis providing ethylbenzene and ammonia, making the quantification of PEA difficult. This can be clearly ruled out based on our independent study of the hydrogenolysis of PEA in many different solvents, see Supporting Information, page 13, showing that this is not the case.
[24] A. N. Parvulescu, P. A. Jacobs, D. E. De Vos, *Chem. Eur. J.* **2007**, *13*, 2034–2043.
[25] T. C. Nugent, M. N. Umar, A. Bibi, *Org. Biomol. Chem.* **2010**, *8*, 4085–4089.

