Organic Process Research & Development

Review

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Large-Scale Carbonyl Reductions in the Pharmaceutical Industry

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ABSTRACT: Herein we present a review on methods for carbonyl reductions on large scale (≥100 mmol) applied to the synthesis of drug candidates in the pharmaceutical industry. We discuss the most common and reliable methods for the reduction of aldehydes, ketones, carboxylic acids, esters, amides, imides, and acid chlorides. Representative examples illustrate detailed reaction and workup conditions and highlight the advantages and limitations of each reducing agent with special emphasis on safety, cost, and amenability to scale-up.

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1. INTRODUCTION

Reductions and oxidations are among the most important and prevalent transformations in organic chemistry. In the pharmaceutical industry, the synthesis of drug candidates often requires functional group manipulations via reductants or oxidants during the early stages of compound preparation. Successful compound progression requires greater quantities of active pharmaceutical ingredient (API), and process chemists are responsible for the manufacture of high-quality API under the guidelines of current Good Manufacturing Practices (cGMP) to meet the stringent requirements for clinical testing. As a result, early synthetic routes are often revised for safe and efficient implementation on large scale.

One goal of process development is redox economy,[1] or the minimization of changes to oxidation states throughout a synthesis. For this reason, there is a strong preference to design process routes from raw materials having the desired oxidation states; however, the increasing complexity of drug candidates makes it impossible to avoid reductions or oxidations in process chemistry. Reductions are preferred to oxidations on large scale, as the latter can be more difficult to implement due to process safety and toxicity concerns surrounding many oxidants (which can make the disposal of waste streams difficult and expensive).[2] As a result, reductions are much more frequent than oxidations for the synthesis of pharmaceuticals on large scale and, as many examples in this review will showcase, can be implemented reliably on multikilogram scale.

Both industry and academia place special emphasis on carbonyl reductions due to the versatility of this transformation for the generation of a wide range of products.[3] Hydrogen gas is the ideal reducing agent in terms of cost and atom efficiency, and has very broad applicability for the reduction of carbonyls. Hydrogenation chemistry is well established (first catalytic example reported in 1874 for olefin reduction[4]) and reliable, and typically affords reduction products in high yield and purity with minimal workup.[5] Its drawbacks include the flammability of H_2 gas, the frequent need for specialized equipment, and the lack of reactivity toward certain carbonyl groups (e.g., carboxylic acids, esters, amides). The discovery of $LiAlH_4$ in 1947 (prepared by treating $AlCl_3$ with LiH)[6] and $NaBH_4$ in 1953 (prepared by treating $B(OMe)_3$ with NaH)[7] set the foundation for the development of new and more chemoselective reagents that have considerably expanded the scope of reducing agents.[8] For example, reductions using boron-based reagents now comprise a mature technology routinely

Received: December 23, 2011
Published: February 14, 2012

   dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156–1184

implemented in the pharmaceutical industry with numerous applications in process chemistry where robustness and reliability are fundamental.[9] Further research in this field has led to the development of chiral reagents for asymmetric reductions.[10]

To the best of our knowledge, a general review covering large-scale processes for carbonyl reduction has not been published. Herein we intend to describe technologies that are reliable and well-established or have the possibility of being useful for carbonyl reduction on large scale. For easy reference, this review has been divided into sections and subsections based on functional group conversion (e.g., aldehyde to alcohol). Each subsection contains an introduction citing all the examples we found for a given transformation that meet the following two criteria: (a) implementation on at least 100 mmol scale and (b) the presence of a detailed experimental procedure. The body of each subsection then contains representative examples which highlight the most commonly employed methods for substrate reduction. These examples have been selected because the researchers provided details on decisions leading to the development of reaction and quench conditions. We captured this information in the schemes and text of this review and, where appropriate, commented on the advantages and limitations of processes with respect to safety, cost, and amenability to scale-up. In reaction schemes, Roman numerals indicate steps performed within a single process (e.g., i. LAH; ii. MeOH quench), whereas Arabic numerals designate discrete transformations separated by reaction workups or product isolations.

We have thoroughly reviewed the mainstream, large-scale literature from the early 1990s through December 2011 and believe that we have captured most of the examples from the past 20 years. The patent literature has not been covered in this review since, in our opinion, the most representative examples have been reported in the mainstream literature.

2. ALDEHYDE REDUCTION

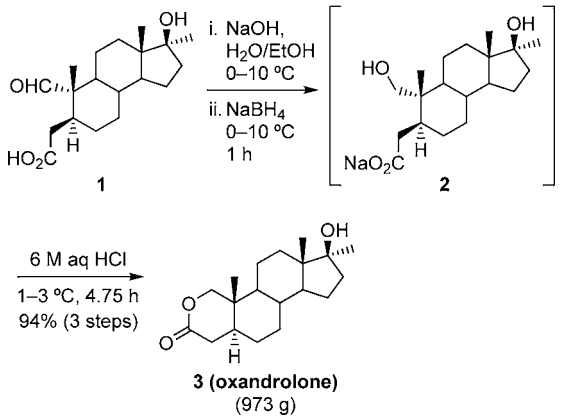
2.1. Aldehyde Reduction to Alcohol. Surprisingly, the reduction of aldehydes to alcohols is not commonly found in the process literature.[11] Sodium borohydride is the preferred reagent for this transformation on large scale since it is reliable, commercially available in bulk and in various forms (powder, pellets, caustic solution), and cost efficient (least expensive metal hydride on a hydride equivalent basis).[12] $NaBH_4$ reductions of aldehydes are typically carried out in THF, alcohols (MeOH, EtOH), or combinations thereof, and may be performed under aqueous or anhydrous conditions. Other solvent combinations include toluene/MeOH[11j] and MTBE/H_2O (biphasic mixture with n-Bu_4NCl as phase-transfer agent).[11i] Sodium hydroxide is sometimes added to stabilize the reagent and avoid decomposition (and the need for a large excess) in protic solvents such as MeOH.

An aqueous quench, sometimes acidic depending on product stability (e.g., HCl,[11b,d] H_2SO_4[11j]), typically follows $NaBH_4$ reduction to destroy residual borohydride. Safety concerns with aqueous quench include hydrogen gas evolution and concurrent exotherm, and acetone may be employed as an alternative quench reagent to avoid offgassing and minimize heat generation.[11i,13] Acetic acid is another alternative when anhydrous quench conditions are required.

The versatility of $NaBH_4$ for the large-scale reduction of aldehydes to alcohols has been demonstrated in the literature.[11] For example, $NaBH_4$ has been used to convert the aldehyde generated from alkene ozonolysis directly to the alcohol.[11f,g] This reagent has also been employed for the reduction of a lactol to the corresponding diol (CH_2Cl_2/MeOH mixture at reflux).[14]

Cabaj and co-workers at Cedarburgh Pharmaceuticals have described the synthesis of anabolic steroid oxandrolone (**3**), a compound to promote weight gain and relieve the bone pain caused by osteoporosis (Scheme 1).[11d] The lactone of the

Scheme 1. Synthesis of oxandrolone (3) via aldehyde reduction with $NaBH_4$ followed by lactonization



molecule was assembled in a one-pot, three-step sequence that started with the sodium salt formation of acid **1** via treatment with aqueous, ethanolic NaOH. The resulting solution was dosed with $NaBH_4$ at 0−10 °C (added in four portions) to reduce the aldehyde group to the corresponding alcohol. Alternatively, a commercially available caustic solution of $NaBH_4$ could be employed, which is more easily handled on scale. After complete reduction of aldehyde to alcohol, 6 M aqueous HCl was added to quench excess $NaBH_4$ and promote the cyclization to the lactone. Oxandrolone (**3**) was then collected by filtration in 94% yield. This material could be further purified by performing a charcoal treatment in MeOH followed by recrystallization from MeOH/H_2O (85% yield). The researchers mentioned that when the reduction was carried out in water, product filtration after acidification was very slow.

In addition to sodium borohydride, both LAH (conversion of an α,β-unsaturated aldehyde to the allylic alcohol; THF, −78 °C, basic quench)[15] and catalytic hydrogenation (conversion of furan-2-carbaldehyde to 2-hydroxymethyltetrahydrofuran, 60 psig, Ra-Ni, MeOH, 60 °C)[16] have been employed for the large-scale reduction of aldehydes to alcohols. The Meerwein−Ponndorf−Verley reduction (IPA/Al(Oi-Pr)$_3$)[17] is another useful method that has not yet been reported in the mainstream literature for the large-scale reduction of aldehydes, although an example for ketone reduction has been reported (section 3.2). As a special case of aldehyde reduction, an interesting example of diastereoselective pinacol homocoupling of an aldehyde to a vicinal diol mediated by VCl_3 has been described by researchers at Hoechst AG.[18]

2.2. Aldehyde Reduction to Alkane. Aldehydes can also be reduced to alkanes, although this transformation rarely appears in the large-scale literature. An example is the reduction of benzaldehyde **4** to toluene **6**, reported by Connolly and co-workers at Roche Palo Alto LLC en route to benzoic acid **9** (Scheme 2).[19] Aldehyde **4** was hydrogenated at 5 psig with 10% Pd/C (5 wt%; 50% water-wet) in EtOAc to provide transient benzylic alcohol **5**, which upon further reduction afforded dimethoxytoluene **6**. Initial experiments with only 2.5 wt% catalyst showed quick reduction to alcohol **5** followed by slow conversion to the alkane over 48 h. The amount of catalyst was

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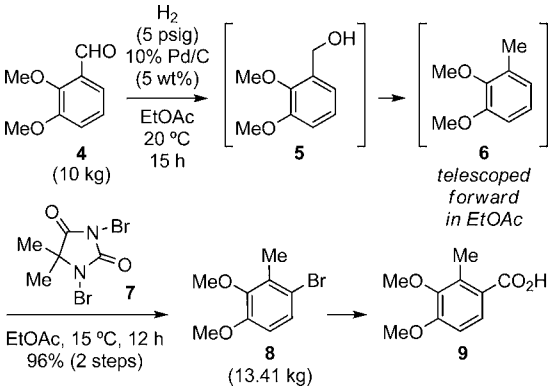
Scheme 2. Benzaldehyde 4 reduction to alkane 6 via catalytic hydrogenation



doubled in the plant to decrease the reaction time; as a result, the aldehyde was fully consumed after 3 h with only 4% residual alcohol **5**. After 15 h, essentially complete reduction of **5** to toluene **6** was observed (only 0.4% of residual **5**). After filtration through Celite or Solka-Floc (cellulose), the EtOAc solution of **6** underwent bromination with 1,3-dibromo-5,5-dimethylhydantoin (**7**) to provide aryl bromide **8**. This material was isolated via crystallization from H_2O/MeOH in 96% yield on multikilogram scale.

3. KETONE REDUCTION

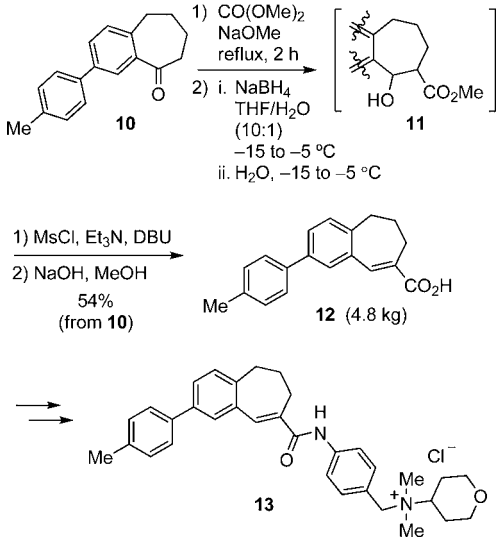
The large-scale reduction of ketones to alcohols in both nonasymmetric and asymmetric fashion is a very general practice and numerous examples can be found in the literature. In particular, the preparation of chiral, secondary alcohols with high optical purity from prochiral ketones is of paramount importance, and many methods are currently available to medicinal and process chemists,[20] including biocatalysis.[20h,21] In this review, the asymmetric reductions have been divided into two categories: substrate-controlled and reagent-controlled.

3.1. Nonasymmetric Ketone Reduction to Alcohol. Sodium borohydride[12] is the preferred reagent for large-scale ketone reductions[22] for the same reasons described in section 2.1. LAH has been employed as an alternative to $NaBH_4$ for large-scale ketone reduction,[23] but the lower chemical selectivity of this reagent limits its application to relatively simple substrates. Dowpharma reported ketone hydrogenation in IPA using (diphosphine)$RuCl_2$(diamine) precatalysts and KO*t*-Bu[24] as a practical alternative to $NaBH_4$.

Ikemoto and co-workers at Takeda Chemical Industries in Japan have reported the preparation of non-peptide CCR5 antagonist candidate **13** for the therapy of HIV-1 (Scheme 3).[22h] During the one-pot preparation of α,β-unsaturated acid **12** from cycloheptanone **10**, an intermediate β-keto ester (not shown) was synthesized by treating **10** with dimethyl carbonate and NaOMe at reflux. Initial conditions ($NaBH_4$ in CH_2Cl_2) for ketone reduction produced the desired β-hydroxy ester **11** with 1,3-diol as a byproduct from ester reduction, and as a result, the purification of **11** required chromatography. Alternatively, ketone reduction in a 10:1 THF/H_2O mixture at −15 to −5 °C provided alcohol **11** without diol after water dilution and product extraction into diisopropyl ether.[25] Dehydration of the β-hydroxy ester via mesylate elimination and subsequent saponification via aqueous NaOH in MeOH provided acid **12** in 54% yield from **10** on kilogram scale.

3.2. Substrate-Controlled, Diastereoselective Ketone Reduction to Alcohol. $NaBH_4$ is also the most widely used

Scheme 3. $NaBH_4$ reduction of β-keto ester intermediate en route to α,β-unsaturated acid 12



reagent for the substrate-controlled, diastereoselective reduction of ketones.[26] This reagent has been used in combination with additives such as $CeCl_3$ (Luche reduction of an enone to allylic alcohol)[27] and Et_3B[28] or Et_2BOMe[11c] (reduction of β-hydroxy ketone to *syn*-1,3-diol). $NaBH_4$ has also been employed for the kinetic resolution of a mixture of diastereomeric, α-substituted cyclopentanones.[26c]

Acyloxyborohydrides, prepared from the reaction of $NaBH_4$ and carboxylic acids, are also useful reagents for diastereoselective, substrate-controlled reductions.[29,30] An attractive feature of these reductants is that their reactivity can be fine-tuned by adjusting the stoichiometry of carboxylic acid (1−3 equiv). Among them, $Me_4N(OAc)_3BH$ is known to reliably afford *anti*-1,3-diols with high diastereoselectivity via reduction of the corresponding β-hydroxy ketones,[31] but we only found a single application of this technology in the process literature.[32]

LAH is a cost-effective reagent, but it is less frequently used for the reduction of ketones to alcohols due to its lower chemical selectivity.[33] Solid LAH is highly flammable and may ignite in moist or heated air. Commercial LAH solutions in various solvents (e.g., THF, 2-methoxyethyl ether, DME) are safer and more practical alternatives for large-scale manufacturing, but careful quenching of LAH reductions with protic solvent is still required to control the rate of H_2 evolution and accompanying exotherm. In addition, aluminum salts often complicate reaction workup and product isolation, but the Fieser conditions[34] generally precipitate these salts from solution as a granular solid that can be easily removed by filtration.

Diisobutylaluminum chloride (DIBAC)[35] is a less known alternative to DIBAL, and only one example has been found in the large-scale literature for substrate-controlled, diastereoselective ketone reduction.[36] Another technology that has received little attention from the process community, despite being cost-effective and environmentally friendly, is the Meerwein−Ponndorf−Verley reduction.[17,37] This method employs $Al(Oi\text{-}Pr)_3$ as catalyst and IPA (a readily oxidized secondary alcohol) as solvent to generate acetone as byproduct, which can be easily removed by distillation to drive the reaction to completion.

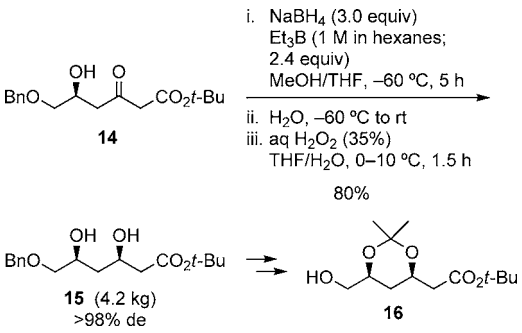
Other reagents and methods implemented on large-scale for substrate-controlled, diastereoselective ketone reduction to

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

alcohol are L-Selectride (cyclohexenone reduction to allylic alcohol during the synthesis of anti-Alzheimer drug (−)-galanthamine),[38] catalytic hydrogenation in the presence of PtO_2 (cyclohexanone reduction in steroid substrate),[39] and $Li(Ot\text{-}Bu)_3AlH$ (aliphatic ketone reduction during the synthesis of HIV protease inhibitor atazanavir).[40]

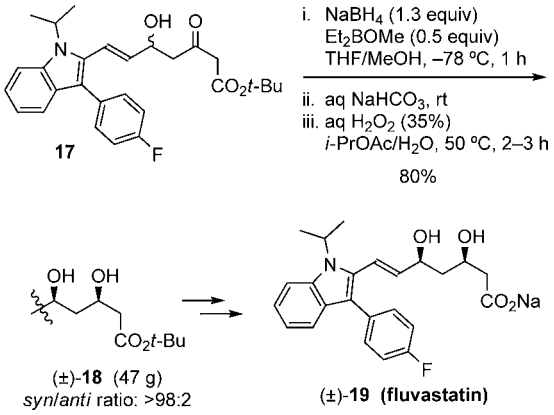
Beck and co-workers at Hoechst AG in Germany combined $NaBH_4$ with Et_3B (1 M in hexanes) to reduce β-hydroxy ester **14** to *syn*-1,3-diol **15**, an intermediate to side-chain **16** for 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (Scheme 4).[28] Similarly, Fuenfschilling and

Scheme 4. Diastereoselective ketone reduction with $NaBH_4$/Et_3B during the synthesis of HMG-CoA reductase inhibitors side-chain 16



co-workers at Novartis combined $NaBH_4$ with $Et_2B(OMe)$ (50% in THF) to prepare the racemic *syn*-1,3-diol **18** for the synthesis of racemic fluvastatin (**19**, Scheme 5).[11c] Both cases

Scheme 5. Substrate-controlled ketone reduction with $NaBH_4$/Et_2BOMe en route to (±)-fluvastatin (19)



required cryogenic temperatures and provided *syn*-1,3-diols with high diastereoselectivities after aqueous quench and oxidative workup to cleave the initial boronate from reduction.

The Evans–Saksena reduction[31] of β-hydroxy ketone **20** was implemented by researchers at Novartis for the large-scale preparation of the anticancer marine natural product discodermolide (**22**, Scheme 6).[32] The highly functionalized and advanced intermediate **20** was treated with $Me_4N(OAc)_3BH$ at −25 °C in a mixture of THF and glacial AcOH. After an 18-h period at 0 °C, the reaction was quenched with an aqueous solution of sodium potassium tartrate (Rochelle salt). Workup and chromatography afforded *anti*-1,3-diol **21** in 73% yield and high diastereoselectivity (exact information on stereoselectivity was not provided in the article).

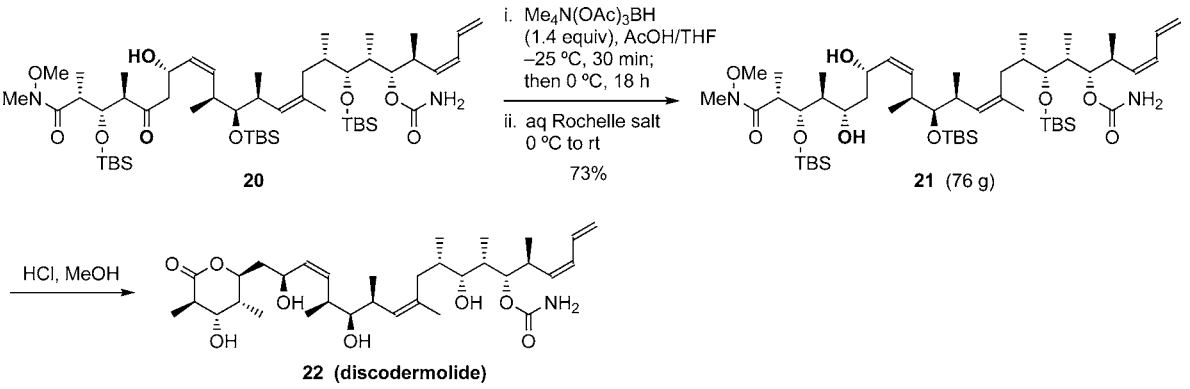
Watson and co-workers at the Hoechst Marion Roussel Research Institute used LAH to effect the diastereoselective reduction of cyclopentenone **23** to allylic alcohol **24** for their synthesis of **25** (MDL 201449A), a candidate for the treatment of multiple inflammatory diseases (Scheme 7).[33b] A solution of cyclopentenone **23** in MTBE was added to a mixture of LAH and LiI in toluene while maintaining batch temperature between −30 and −20 °C. The additive LiI served two purposes: (a) it suppressed 1,4-hydride addition to **23**, thus minimizing olefin reduction byproducts; and (b) it allowed the raising of reaction temperature from −78 to −30 °C. After reaction completion, the mixture was quenched with aqueous NH_4Cl at a rate to maintain an internal temperature below 10 °C. The aluminum salts were removed by filtration, and concentration of the organic layer provided alcohol **24** in 76% yield as a 37:1 mixture of *cis/trans* isomers. Ethereal cosolvents were required for LAH solubility, and initial studies using Et_2O/toluene gave more favorable *cis/trans* ratios; however, the highly flammable and peroxide-forming Et_2O was replaced with MTBE to avoid the process safety risks associated with the diethyl ether. Furthermore, to minimize the handling risks associated with flammable LAH and anhydrous LiI (hygroscopic), both materials were purchased in preweighed, toluene-soluble bags and charged directly to the tank.

Singh and co-workers at Bristol-Myers Squibb employed DIBAC for the reduction of cyclobutanone **26** to alcohol **27** during the preparation of lobucavir (**28**), a potent antiviral agent for the treatment of herpes, hepatitis B, and HIV (Scheme 8).[36] The conversion of cyclobutanone **26** to alcohol **27** was originally carried out with lithium trisiamylborohydride (LS-Selectride) in excellent stereoselectivity, but this reagent is expensive, only commercially available as a THF solution, and generated 5−10% of rearrangement product **29**. When lithium tri-*sec*-butylborohydride (L-Selectride) was employed, the stereoselectivity dropped to 77%. On the other hand, effecting the reduction with DIBAC in CH_2Cl_2 at −40 °C provided alcohol **27** with 92% diastereoselectivity. Greener alternatives to CH_2Cl_2 were evaluated (PhMe, THF), but only dichloromethane provided reproducible diastereoselectivity on scale. Quenching the reaction at low temperature with MeOH prevented the formation of byproduct **29**, and recrystallization from MeOH upgraded the chiral purity to afford **27** in 68% yield and >99% de.

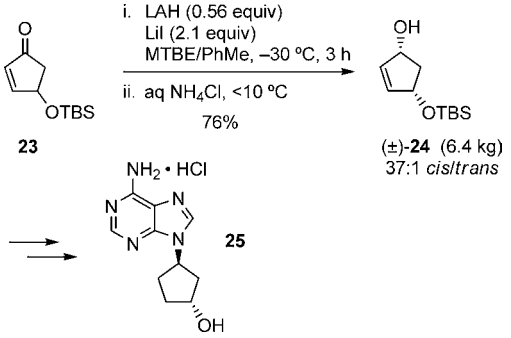
A Meerwein–Ponndorf–Verley (M–P–V) reduction has been employed by Romanczyk and co-workers at Johnson Matthey Pharmaceutical Materials, Inc. and Masterfoods USA for the reduction of ketone **30** to alcohol **31** en route to naturally occurring procyanidins **32** and **33** (Scheme 9).[37] The L-Selectride/LiBr combination at −78 °C in THF was initially tested, but low throughput did not make it amenable for scale-up. As a second option, an extensive screen of catalytic hydrogenation conditions using Ru catalysts and a variety of ligands was performed, but incomplete reactions and low diastereoselectivities were obtained in most cases. The best result was obtained with Ru(II)-(*R*)-BINAP, which afforded alcohol **31** in 82% yield with only 1.5% unreacted **30**, 5% of the undesired diastereomer, and several unidentified impurities. However, when the reduction was carried out in the presence of $Al(Oi\text{-}Pr)_3$ and IPA at reflux (M–P–V conditions), an 89:7 ratio between **31** and the undesired diastereomer was obtained. The byproduct acetone was continuously distilled together with IPA to drive the reduction to completion. Additional IPA was added until HPLC analysis of the reaction mixture showed

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

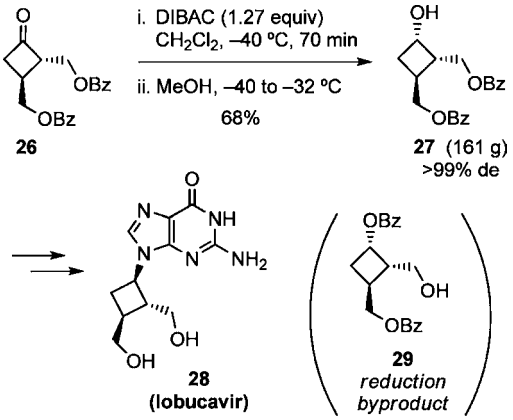
Scheme 6. Diastereoselective Evans–Saksena ketone reduction in the synthesis of discodermolide (22)



Scheme 7. Diastereoselective LAH reduction of cyclopentenone 23



Scheme 8. Substrate-controlled DIBAC reduction of cyclobutanone 26 en route to lobucavir (28)

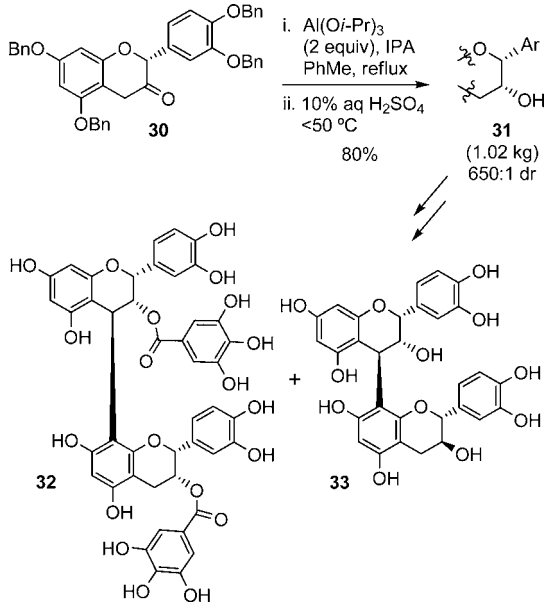


complete consumption of ketone **30**. After an aqueous H_2SO_4 quench and trituration in MeOH, alcohol **31** was obtained in 80% yield and 650:1 dr.

3.3. Reagent-Controlled, Asymmetric Ketone Reduction to Alcohol. Two methods clearly stand out for the reagent-controlled, asymmetric reduction of ketones to alcohols: (a) oxazaborolidine-mediated reduction with boranes;[20a,41] (b) catalytic or transfer hydrogenation in the presence of a chiral Ru catalyst.

Oxazaborolidines derived from (*S*)-prolinol (CBS catalyst)[42] and (1*R*,2*S*)-1-amino-2-indanol[43,44] cover all the examples cited in this review and generally convert ketone to alcohol with good to excellent enantioselectivities. $BH_3{\cdot}SMe_2$ is the most commonly used stoichiometric reducing agent[45] despite the stench problems associated with its large-scale use, such as the need for efficient scrubbing and disposal of large volumes of

Scheme 9. Substrate-controlled Meerwein–Ponndorf–Verley reduction of ketone 30 en route to procyanidins 32 and 33



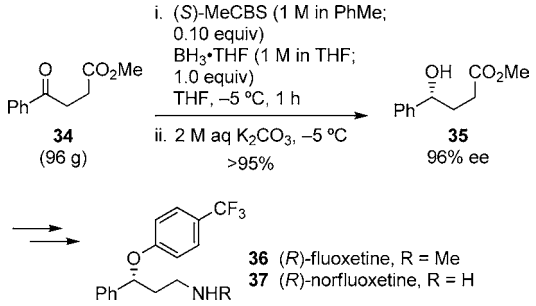
waste contaminated with SMe_2. Other borane sources include $BH_3{\cdot}THF$,[42k] $BH_3{\cdot}Et_2NH$,[42g] catecholborane,[42d] and $BH_3{\cdot}Et_2NPh$.[42b,e,44a] $BH_3{\cdot}$amine complexes[46] offer several process advantages: (a) storage at ambient temperature (unlike $BH_3{\cdot}THF$ which requires refrigeration);[47,48] (b) lack of stench (unlike $BH_3{\cdot}SMe_2$); (c) lack of pyrophoricity. In addition, reagents such as $BH_3{\cdot}Et_2NPh$ are sold at higher concentrations, which permits increased throughput in the plant. Strictly anhydrous conditions are required to obtain high enantioselectivities since even very slight amounts of water can have a huge impact on the selectivity of asymmetric reduction.[42l] Also, variable enantioselectivities have been reported when using commercial boranes in conjunction with CBS catalyst.[42l]

Oxazaborolidine reductions are typically quenched with water, alcohol, or acid. Another option is an oxidative quench with 30% aqueous H_2O_2 which forms borate byproducts and oxidizes SMe_2 to DMSO (when using $BH_3{\cdot}SMe_2$). α-Halo ketones (Cl or Br) are common substrates which provide a handle for subsequent epoxide formation or the introduction of additional functionality by halogen displacement with nucleophiles.[42a,e,g,j,44]

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156–1184

Senanayake, Lu, and co-workers at Sepracor have described the preparation of (*R*)-fluoxetine (**36**), one of the enantiomers of Prozac, and its metabolite (*R*)-norfluoxetine (**37**) (Scheme 10).[42k]

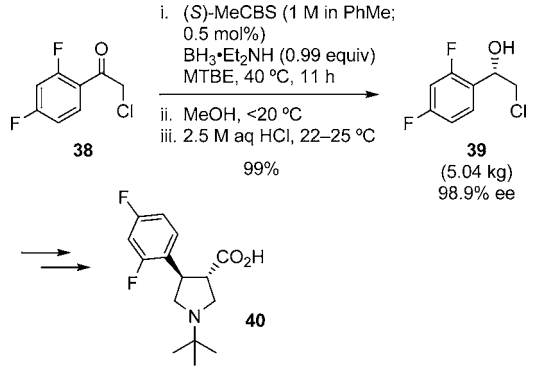
Scheme 10. Oxazaborolidine reduction of ketone 34 during the synthesis of (*R*)-fluoxetine (36) and (*R*)-norfluoxetine (37)



Several approaches were investigated for the asymmetric reduction of ketone **34**. Catalytic hydrogenation with Noyori's BINAP-Ru(II) catalyst required harsh conditions (1500 psig, 35 °C), and only 30% conversion was observed after 11 days. Alternatively, (+)-Ipc_2BCl (prepared in situ from α-pinene (87% ee), $NaBH_4$, and BCl_3) in DME provided excellent enantioselectivity (97% ee) with subsequent lactone formation; however, this reagent is expensive and inconvenient for large scale due to difficulties removing α-pinene byproducts. The best results (>95% yield, 96% ee) were obtained when BH_3·THF (1 M in THF) and ketone **34** were simultaneously added to a solution of (*S*)-MeCBS (10 mol%; 1 M in toluene) in THF at −5 to 0 °C. After aqueous K_2CO_3 quench and workup, crude alcohol **35** was isolated and used in the next step without further purification.

Chung and co-workers at Merck have utilized a (*S*)-MeCBS-catalyzed reduction in combination with BH_3·Et_2NH for the synthesis of pyrrolidine-3-carboxylic acid **40** (Scheme 11).[42g]

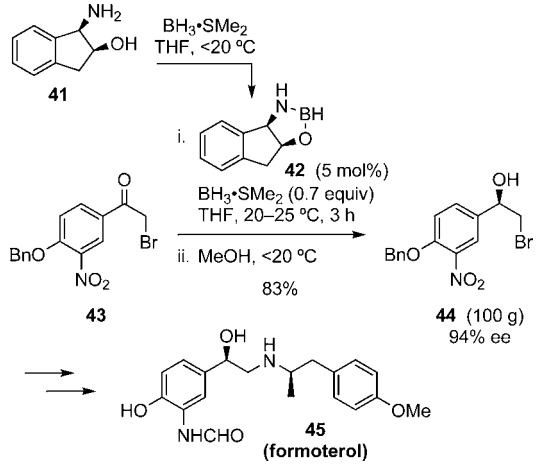
Scheme 11. Oxazaborolidine-mediated reduction of α-chloro ketone 38 en route to chiral pyrrolidine 40



A solution of α-chloro ketone **38** in MTBE was added over 10 h to a heated mixture of borane complex and oxazaborolidine (1 M in toluene) in MTBE at 40 °C. After the complete dosing of **38**, the mixture was held at 40 °C for another hour and allowed to cool to 18 °C overnight, which generated alcohol **39** in excellent yield and optical purity. Although (*S*)-MeCBS-catalyzed reductions typically require cryogenic temperatures as low as −50 °C for satisfactory enantioselectivities, much better results were obtained in this case at higher temperatures with as little as 0.5 mol% of the (*S*)-MeCBS catalyst. In addition, the lower-boiling MTBE was chosen as solvent instead of toluene to avoid codistillation of alcohol **39** during workup. After subsequent quenches with MeOH and aqueous HCl, **39** was obtained in ~99% ee as an oil that solidified upon cooling to −5 °C. Alternatively, asymmetric transfer hydrogenation with [cymene]RuCl[*R*,*R*-TsDPEN] in $MeOH/HCO_2H/Et_3N$ provided **39** in only 86% ee. The enantioselectivity increased to 91% ee when bulkier hexamethylbenzene was employed as ligand, but still well below the outcome obtained with (*S*)-MeCBS.

A similar substrate was used by Hett, Gao, and co-workers at Sepracor during the synthesis of formoterol (**45**), a long-acting, very potent β_2-agonist for the treatment of asthma and chronic bronchitis (Scheme 12).[44b] The reduction of α-bromo ketone

Scheme 12. Asymmetric reduction of ketone 43 mediated by indanol-derived oxazaborolidine 42



43 was initially carried out with *B*-methyloxazaborolidine **46** (Figure 1), prepared from (1*R*,2*S*)-1-amino-2-indanol (**41**) and

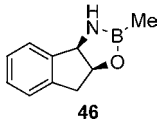


Figure 1. *B*-methyloxazaborolidine **46** for reduction of ketone **43**.

trimethylboroxin ($(Me_3BO)_3$), and BH_3·THF as a stoichiometric reductant. However, the cost, operational complexity, and the need for cryogenic conditions (−15 °C) and 20 mol% catalyst ruled out this combination despite achieving alcohol **44** with good enantioselectivity (95% ee). Instead, the researchers investigated ketone reduction with oxazaborolidine **42**, which is easier to prepare than **46** and does not require expensive starting materials. Catalyst **42** was generated from **41** and two equivalents of BH_3·SMe_2 in THF (<20 °C), and then α-bromo ketone **43** and additional BH_3·SMe_2 were added simultaneously over 3 h. After reaction completion (15 min), MeOH quench followed by acidic workup and recrystallization from heptane/toluene afforded (*R*)-alcohol **44** in 83% yield and 94% ee. A second recrystallization from heptane/toluene increased the chiral purity to >99.5% ee.

Another common method for reagent-controlled, asymmetric ketone reduction is hydrogenation in the presence of H_2[28,49] or hydrogen donors such as IPA or HCO_2H (i.e., transfer hydrogenation).[42i,50] Hydrogenation under an atmosphere of H_2 is

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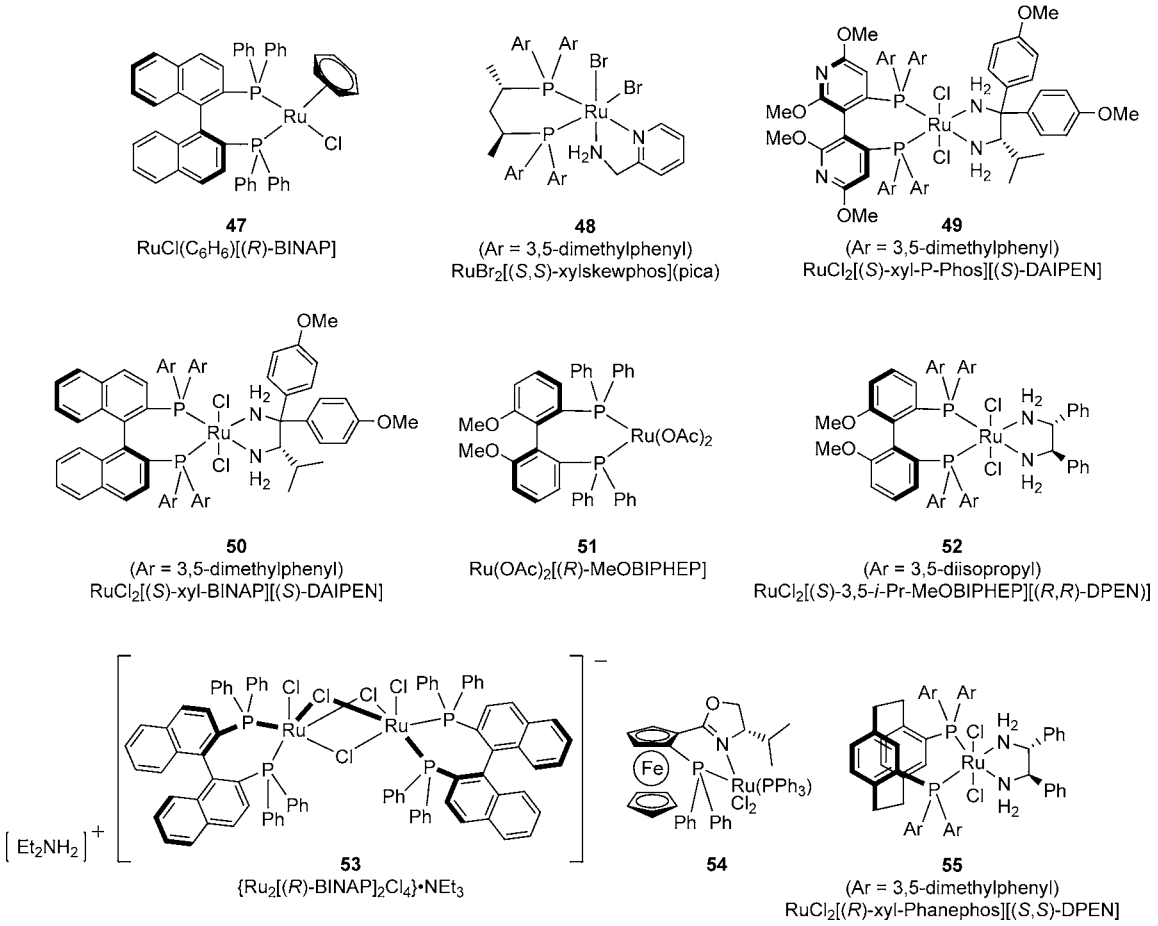
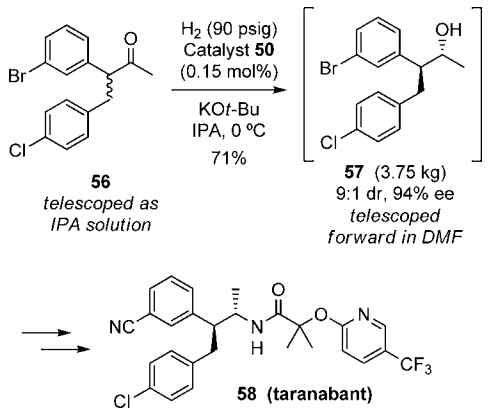


Figure 2. Chiral Noyori-type catalysts for the asymmetric hydrogenation of ketones.

more prevalent than transfer hydrogenation, with Noyori-type catalysts such as $RuCl(C_6H_6)[(R)\text{-BINAP}]$ (**47**),[28] $RuBr_2[(S,S)\text{-XylSkewphos}](pica)$ (**48**),[49b] $RuCl_2[(S)\text{-Xyl-P-Phos}][(S)\text{-DAIPEN}]$ (**49**),[49c] $RuCl_2[(S)\text{-Xyl-BINAP})][(S)\text{-DAIPEN})]$ (**50**),[49d] $Ru(OAc)_2[(R)\text{-MeOBIPHEP}]$ (**51**),[49e] $RuCl_2[(S)\text{-3,5-}i\text{-Pr-MeOBIPHEP}][(R,R)\text{-DPEN})]$ (**52**),[49h] $\{Ru_2[(R)\text{-BINAP}]_2Cl_4\}\cdot NEt_3$ (**53**),[49i] and $\{Ru_2[(S)\text{-BINAP}]_2Cl_4\}\cdot NEt_3$,[49g] reported in the literature (Figure 2). Chiral (phosphinoferrocenyl)oxazoline ligand **54** has also been employed on pilot-plant scale.[49f] Catalyst cost may be an issue on large scale, despite low catalyst loadings and the formation of alcohol products with high stereoselectivity.

Chen and co-workers at Merck have described the preparation of taranabant (**58**), a potent, selective, and orally bioavailable cannabinoid-1 receptor inverse agonist candidate for the treatment of obesity (Scheme 13).[49d] The two chiral centers on the molecule were introduced by means of a dynamic kinetic resolution of racemic ketone **56** to alcohol **57** under hydrogenation conditions in the presence of KO*t*-Bu and Noyori's catalyst $RuCl_2[(S)\text{-Xyl-BINAP})][(S)\text{-DAIPEN})]$ (**50**, Figure 2). An extensive study of reaction conditions was carried out to optimize **57** with respect to enantiomeric excess and diastereoselectivity. IPA provided better diastereoselectivity but with 2% lower enantiomeric excess than 2-BuOH. Lowering the temperature from 20 to 0 °C increased overall selectivity for **57**, whereas higher hydrogen pressures and base loadings had no effect on the stereoselectivity. Water had a deleterious effect on the reaction rate and anhydrous conditions (≤500 ppm H_2O) were required for reproducible results. The catalyst loading was

Scheme 13. Dynamic, kinetic resolution of ketone 56 with Noyori's catalyst $RuCl_2[(S)\text{-Xyl-BINAP}][(S)\text{-DAIPEN}]$ (50)



optimized to 0.15 mol% Ru, as higher loadings increased the reaction rate at the expense of lower selectivities. Catalyst $RuCl_2[(R)\text{-Xyl-Phanephos}][(S,S)\text{-DPEN}]$ (**55**) also provided **57** with excellent selectivity (88% ee, 23:1 dr) at 0.1 mol% loading after 24 h at 0 °C and thus proved itself a possible substitute for **50**. On kilogram scale, prior to cooling and H_2 pressurization, the catalyst was activated by aging for 3 h in a solution of racemic ketone and KO*t*-Bu in IPA. The reactor was then cooled to 0 °C over 4−5 h, and the reduction was executed under 90 psig H_2. After reaction completion, a series of solvent switches and aqueous workup afforded a DMF

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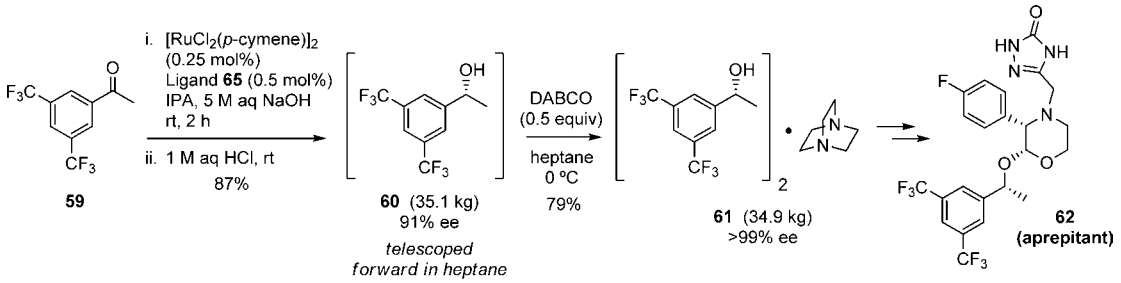
Scheme 14. Asymmetric hydrogenation of ketone 59 with $[RuCl_2(p\text{-cymene})]_2$/(1*S*,2*R*)-1-amino-2-indanol (65)



solution of alcohol **57** that was used in the next step without further purification.

Researchers at Merck have published two articles on the reduction of 3,5-bistrifluoromethyl acetophenone (**59**) to chiral benzyl alcohol **60** via asymmetric transfer hydrogenation en route to aprepitant (**62**), an NK-1 receptor antagonist for the treatment of chemotherapy-induced emesis (Scheme 14).[42i,50d] Combinations of metal catalysts ((dichloro-pentamethyl-cyclopentadienyl)Rh(III) dimer, dichloro(*p*-cymene)Ru(II) dimer) and ligands ((1*R*,2*R*)-TsCYDN (**63**), (1*R*,2*R*)-TsDPEN (**64**), and (1*S*,2*R*)-1-amino-2-indanol (**65**); Figure 3) were

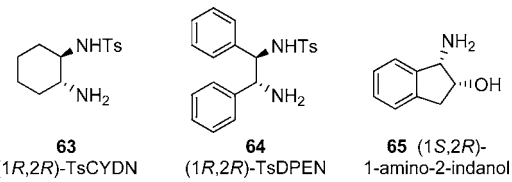


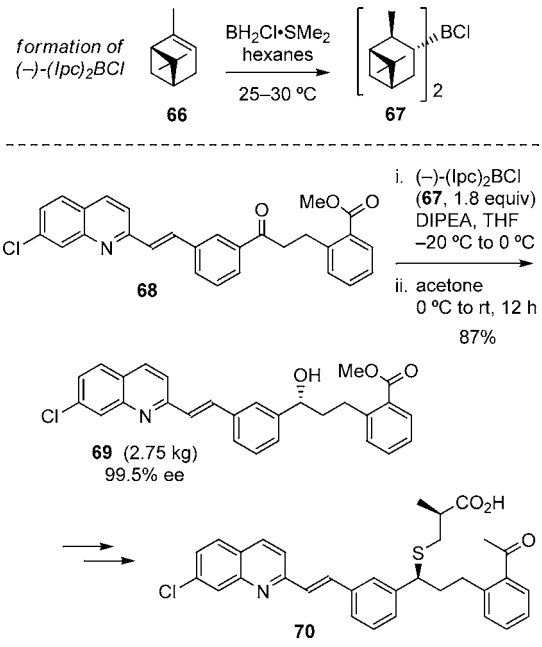
Figure 3. Chiral ligands tested during asymmetric reduction of ketone **59**.

evaluated for the reduction of **59**. The pair of $[RuCl_2(p\text{-cymene})]_2$ and ligand **65** was chosen for development, as the ligand was readily available at Merck, and this catalyst system reliably afforded alcohol **60** on multikilogram scale. Alternative ligand (1*R*,2*R*)-TsCYDN (**63**) also provided alcohol **60** with high chiral purity (94% ee) but required high dilution (0.1 M), and the ligand was not commercially available at the time of scale-up. The transfer hydrogenation performed well in the presence of aqueous bases and was not air-sensitive. As little as 0.25 mol% catalyst gave complete conversion in pilot runs, but 0.5 mol% was chosen on large scale to ensure robustness. A simple process was developed in which a mixture of Ru catalyst and ligand **65** was aged in IPA for 1 h followed by the addition of ketone **59** and additional IPA. The ketone was consumed within 2 h at rt; following an aqueous HCl quench, alcohol **60** was extracted into heptane in 87% yield and 91% ee. Since this material was difficult to purify by crystallization, an inclusion complex with DABCO was formed after adding this base to the heptane solution of crude alcohol. Complex **61** was crystallized and isolated in 79% yield and >99% ee. The enantiomerically pure alcohol could then be isolated by dissolving **61** in an organic solvent and extracting DABCO into aqueous acid washes.

B-Chlorodiisopinocamphenylborane (i.e., Ipc_2BCl or DIP-Cl), either from commercial sources or prepared in situ from α-pinene and $BH_2Cl{\cdot}SMe_2$, is a reducing agent that has been employed for the asymmetric reduction of alkyl aryl ketones.[51] Since both (+)-α-pinene and (−)-α-pinene are commercially available,[52] Ipc_2BCl reductions can prepare either enantiomer of the desired alcohol. However, this method has lost popularity in recent years to more modern alternatives. Reasons for the decline of Ipc_2BCl reductions on process scale include the need for stoichiometric amounts of reagent and difficulties removing pinene-related byproducts without chromatography.[51b] Acetone can be employed for nonaqueous quench, and in some cases boron byproducts may be removed by adding an amine (e.g., diethanolamine) to form a water-soluble boron-amine complex for aqueous extraction or filtration.[53]

King and co-workers at Merck have reported the preparation of compound **70**, a specific LTD_4 antagonist for the treatment of asthma (Scheme 15).[51d] The benzylic stereocenter of the

Scheme 15. (−)-Ipc_2BCl-mediated, asymmetric reduction of ketone 68



API was set via asymmetric reduction of ketone **68** to the corresponding (*R*)-alcohol **69**. Initially, oxazaborolidine-borane complexes provided **69** with excellent enantioselectivity (98.5% ee); however, partial reduction of the ethylene bridge was observed (3−10%) due to trace Pd from a previous Heck coupling. Olefin reduction could be considerably suppressed by increasing the oxazaborolidine loading from 20 mol% to 55 mol%; however, this was impractical as the oxazaborolidine had to be prepared in five steps. As an alternative, it was discovered that (−)-Ipc_2BCl (**67**), generated readily and inexpensively by treating (−)-α-pinene (**66**) with $BH_2Cl{\cdot}SMe_2$ in hexanes, provided alcohol **69** with slightly lower selectivity (97.8% ee) but with less than 1% olefin reduction. On kilogram

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

scale, (−)-Ipc_2BCl (1.8 equiv) was added slowly to a solution of ketone and diisopropylethylamine in THF while maintaining a batch temperature between −25 and −20 °C, and the resulting mixture was held at −20 °C for 3.5 h before warming to 0 °C and quenching with acetone. Aqueous workup and crystallization from *i*-PrOAc/H_2O/hexanes afforded alcohol **69** in 87% yield and 99.5% ee. The authors mentioned that when α-pinene of lower chiral purity (70% ee) was employed for ketone reduction, a remarkable asymmetric amplification was observed that resulted in the generation of alcohol **69** in 95% ee.

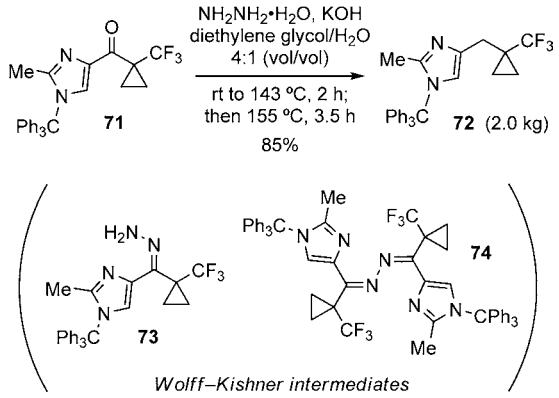
Other reagents for the asymmetric reduction of ketones to alcohols are BINAL-H (prepared from LAH and (*R*)-(+)-1,1′-bi-2-naphthol; diaryl ketone reduction),[54] $NaBH_4$/L-tartaric acid (α-keto acid to α-hydroxy acid),[55] and catalytic hydrogenation with 5% Pt/Al_2O_3 and dihydrocinchonidine as chiral ligand (α-keto ester to α-hydroxy ester).[56]

Although not yet reported on large scale, the combinations of $NaBH_4$ and chiral cobalt complexes,[57] or $NaBH_4$ or $LiBH_4$ and chiral Lewis acid (L)-TarB−NO_2 boronic ester,[58] have potential for future process applications of reagent-controlled, asymmetric ketone reduction.

3.4. Ketone Reduction to Alkane. Although relatively uncommon in process chemistry, the large-scale reduction of ketones to alkanes is more frequent than the analogous reduction for aldehydes. Several conditions are found in the process literature to carry out this transformation on either alkyl aryl ketones or diaryl ketones. The Wolff−Kishner reaction (hydrazine[59]/KOH)[60,61] and silicon-based reducing agents (Et_3SiH,[62] tetramethyldisiloxane[63]) comprise most examples, but Zn/Ac_2O (diaryl ketone),[64] BH_3·THF (diaryl ketone; 50 °C),[65] $NaBH_4$ (alkyl aryl ketone),[66] and catalytic hydrogenation in the presence of 5% Pd/C (alkyl aryl ketone)[56] have also been reported.

A Wolff−Kishner reduction was performed by Kuethe and co-workers at Merck for the multikilogram-scale preparation of imidazole **72** via reduction of cyclopropyl ketone **71** (Scheme 16).[61a] A very thorough screen was undertaken to identify reaction conditions that were compatible with the cyclopropyl group, and radical-based reactions such as Clemmensen or silyl hydride-mediated methods were ruled out. Reagents such as LAH, $NaBH_4$, $LiBH_4$, and $NaCNBH_3$ in combination with a Lewis acid ($AlCl_3$ or BF_3·OEt_2) only afforded the alcohol product, whereas hydrogenation, depending on the reaction conditions, led to cyclopropyl ring-opening, partial reduction to the alcohol, or no reaction whatsoever.

Scheme 16. Wolff−Kishner reduction of ketone 71 to alkane 72



Eventually, the researchers applied Wolff−Kishner conditions in the plant by treating ketone **71** with hydrazine hydrate (8 equiv), KOH (4 equiv), and a controlled amount of water (~0.23 g/g of NH_2NH_2, needed to minimize the amount of hydrazine in the reaction headspace). Upon complete consumption of ketone **71** in diethylene glycol at reflux, HPLC revealed a mixture of desired product **72**, hydrazone **73**, and azine **74**. A portion of water was then removed via Dean−Stark apparatus, the internal temperature rose to 155 °C, and HPLC analysis showed complete conversion of **73** and **74** to alkane **72**. The mixture was cooled and diluted with MeCN and H_2O to crystallize **72** in 85% yield.

Waite and Mason at Pfizer have reported the preparation of thromboxane receptor antagonist **77** for the treatment of asthma, unstable angina, deep vein thrombosis, and coronary atherosclerosis (Scheme 17).[62b] Catalytic hydrogenation was explored without success for the one-pot reduction of both double bonds and carbonyl of **75**. Instead, a two-step protocol was implemented that called for initial ketone reduction by adding a large excess of Et_3SiH (5 equiv) to a solution of **75** in TFA at 10−15 °C. The resulting mixture was allowed to warm to ambient temperature over 12 h, at which point alkane **76** had precipitated from solution and was isolated via filtration in 83% yield. Subsequent olefin hydrogenation with 5% Pd/C generated the two saturated side chains.

During the synthesis of antipsychotic drug ziprasidone hydrochloride monohydrate (**81**), a selective serotonin and dopamine antagonist, Nadkarni and Hallisey at Pfizer reported a one-pot synthesis of 6-chloro-5-(2-chloroethyl)oxindole (**80**) from 6-chlorooxindole (**78**) (Scheme 18).[63] After the $AlCl_3$-mediated Friedel−Crafts acylation of **78** with chloroacetyl chloride, the reaction mixture was cooled to 0−5 °C and dosed with tetramethyldisiloxane (TMDS). After 4−6 h at this temperature, the reaction mixture was quenched with water, and the HCl generated from excess $AlCl_3$ was sequestered by a caustic scrubber. After workup, crystallization from IPA/THF provided the deoxygenated **80** in 87% yield for the two steps combined. An advantage of TMDS, in comparison to longer-chain siloxanes, was that silyl reaction byproducts were easily purged in the organic filtrates.

4. CARBOXYLIC ACID REDUCTION TO ALCOHOL

Several methods have been reported for the reduction of carboxylic acids to alcohols. Borane[47] is a very common reagent for this purpose, either as BH_3·THF (1 M in THF)[67] or BH_3·SMe_2 (usually employed neat on scale, although solutions in various solvents and molarities are commercially available).[68] BH_3·THF is more reactive than BH_3·amine complexes, and it may work for substrates where the latter fails.[67c] An aqueous, acidic workup (e.g., HCl, citric acid) usually follows reduction with BH_3·THF. For reductions with BH_3·SMe_2, THF and CH_2Cl_2 are the solvents of choice, and either aqueous, methanolic KF[68a] or aqueous NaOH quenches have been employed after reaction completion. Acids can be chemoselectively reduced to alcohols with borane in the presence of esters.

In addition to borane, $NaBH_4$ in combination with other reagents such as CDI[69] and ethyl chloroformate[68e,70] (via mixed anhydride formation), $CaCl_2$ (in situ formation of $Ca(BH_4)_2$),[71] HCl,[72] BF_3·OEt_2 (in situ formation of borane),[73] I_2,[74] and H_2SO_4[75] is found in the process literature for the reduction of acids to alcohols. ($NaBH_4$ alone does not reduce acids to alcohols.) THF is the most common solvent for these borohydride reductions, but alternatives such as EtOAc/IPA/H_2O,[70] EtOH,[71]

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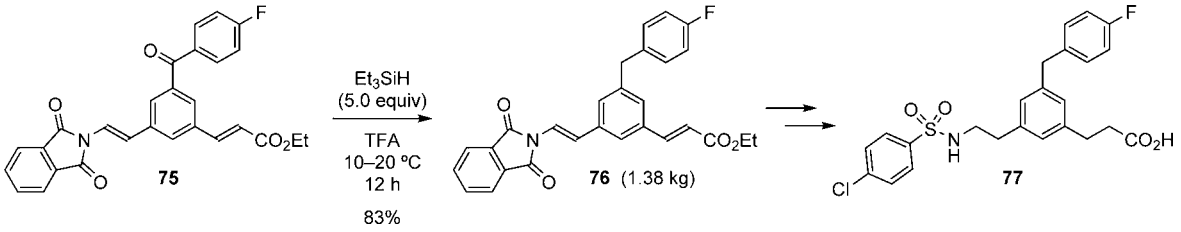
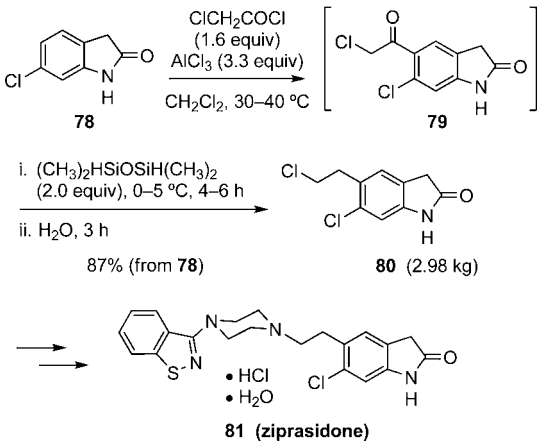
Scheme 17. Ketone 75 reduction to alkane 76 with Et_3SiH/TFA



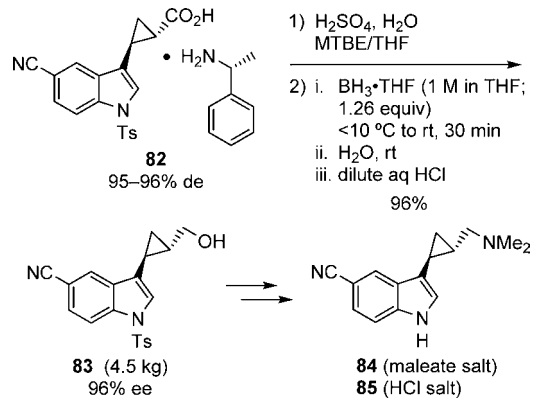
Scheme 18. Tetramethyldisiloxane reduction of ketone 79 en route to ziprasidone HCl monohydrate (81)



diglyme/THF,[72] and *i*-PrOAc[73] have been reported. LAH (1 M in THF)[76] and $LiBH_4$ (2 M in THF)/TMSCl[77] have also reduced acids to alcohols on large scale on relatively simple substrates. Although $LiBH_4$ is an excellent reagent for the reduction of a number of functional groups, its cost may be prohibitive for large-scale applications. Catalytic hydrogenation of acids to alcohols usually requires harsh conditions (high temperature and pressure) that are not compatible with complex molecular functionality and may be difficult to implement in large-scale preparations due to special equipment requirements.

Chen and co-workers at Bristol-Myers Squibb have prepared the maleate and HCl salts **84** and **85**, respectively, as selective serotonin reuptake inhibitors with potential applications in neuroscience (Scheme 19).[67b] The generation of alcohol intermediate **83** was first attempted via direct reduction of (*R*)-(+)-α-methylbenzylamine salt **82** with BH_3·THF, but substantial nitrile reduction was also observed. Alternatively,

Scheme 19. BH_3·THF-mediated reduction of carboxylic acid in 82 to alcohol 83

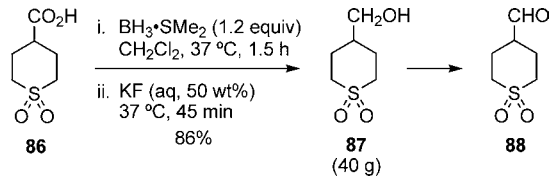


salt splitting with aqueous H_2SO_4 produced the free acid as a MTBE solution, which in turn was treated with BH_3·THF (1 M in THF) to provide alcohol **83** with less than 2% nitrile reduction. The BH_3·THF addition (1.15 equiv) was carried out while holding the internal temperature below 10 °C before warming to 22 °C. After an additional charge of BH_3·THF (0.11 equiv), <1.5% unreacted acid remained, and the mixture was quenched with dilute aqueous HCl. Alcohol **83** was collected by filtration in 96% yield and 96% ee while purging any nitrile reduction byproduct.

Prior to scale-up, calorimetric data revealed the existence of two exotherms during the reduction of the acid of **82**. The first was a consequence of acid deprotonation (with concomitant hydrogen gas evolution) and was dependent on the rate of addition of the reducing agent. The second was the result of the acid reduction and displayed an induction period and heat evolution beyond the completion of BH_3·THF addition. Attempts to increase the reaction rate at higher temperatures were unsuccessful due to increased levels of nitrile reduction, and so the aforementioned low-temperature, dose-controlled protocol was developed and safely implemented in the plant.

Bio and co-workers at Amgen have described the preparation of 1,1-dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde (**88**), a key intermediate in the synthesis of a drug candidate (Scheme 20).[68a]

Scheme 20. BH_3·SMe_2 reduction of acid 86 en route to aldehyde 88

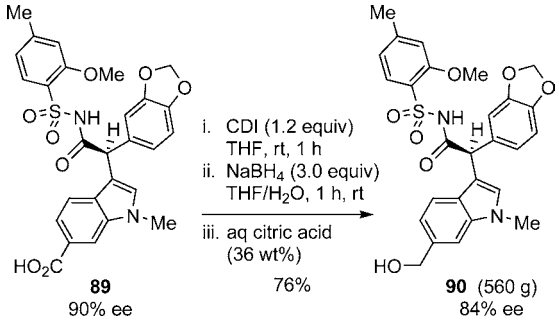


The direct synthesis of aldehyde **88** from acid **86** via reaction with CDI and subsequent reduction of the imidazolide intermediate with DIBAL at −30 °C provided a mixture of **88** and the alcohol over-reduction product **87**. Lowering the temperature to −70 °C for DIBAL reduction suppressed alcohol formation, but the aluminum salts complicated the isolation. As an alternative, a two-step process was implemented in which the first step reduced acid **86** to alcohol **87** using neat BH_3·SMe_2 in CH_2Cl_2 at 37 °C. (BH_3·THF also effected this reduction in THF, but the low solubility of both the acid and alcohol in this solvent gave rise to gummy mixtures that complicated product isolation and purification.) The high water solubility of **87** made an aqueous workup difficult; however, quenching with one equivalent of KF via 50% aqueous solution extracted the boronic acid byproducts into the water phase with minimal loss of alcohol product. Alcohol **87** could be isolated after crystallization from MTBE in 86% yield.

dx.doi.org/10.1021/op2003826 | *Org. Process Res. Dev.* 2012, 16, 1156–1184

Challenger and co-workers at Pfizer in the U.K. have reduced acid **89** to alcohol **90**, an endothelin antagonist with potential application for the treatment of congestive heart failure, pulmonary hypertension, angina, renal dysfunction, restenosis, atherosclerosis, and prostate cancer (Scheme 21).[69] In a one-pot

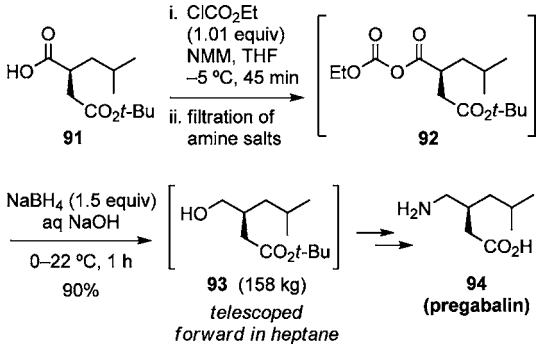
Scheme 21. CDI-mediated $NaBH_4$ reduction of acid 89 en route to 90



process, acid **89** was first treated with CDI in THF to generate an imidazolide intermediate. Epimerization was observed during CDI-activation and could be controlled by limiting the activation time to 1 h before transferring the imidazolide to a solution of $NaBH_4$ in aqueous THF. The reduction was quenched with aqueous citric acid, which was key as alcohol **90** showed some sensitivity to strong acid during the quench and workup, giving rise to a symmetrical ether dimer impurity. By switching from HCl to citric acid (pH 3) and keeping the temperature during the solvent evaporation below 45 °C, this dimeric impurity could be minimized (<5%). Following workup, crystallization from MeOH provided the API in 76% yield and 84% ee.

During the synthesis of pregabalin (**94**, Lyrica), a lipophilic GABA (γ-aminobutyric acid) analogue developed for the treatment of several CNS disorders including epilepsy, neuropathic pain, anxiety, and social phobia, Hoekstra and co-workers at Parke-Davis developed two methods for the reduction of acid **91** to alcohol **93** (Scheme 22).[68e] The first

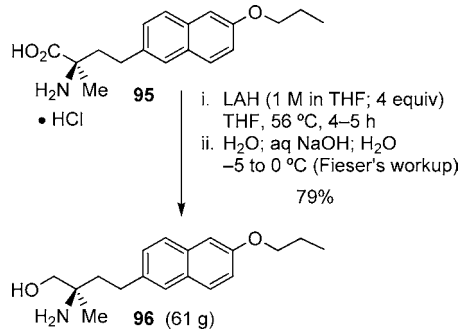
Scheme 22. Acid 91 reduction with $NaBH_4$ via mixed anhydride en route to pregabalin (94)



method employed $BH_3{\cdot}SMe_2$ in MTBE, but efficient scrubbing was required due to the foul smell of dimethyl sulfide. A more process-friendly approach was developed by converting **91** to mixed anhydride **92** with ethyl chloroformate for subsequent reduction via caustic $NaBH_4$ solution. Upon reaction completion and workup, alcohol **93** was isolated as a heptane solution in 90% yield (estimated by gravimetric analysis) that was telescoped to the next step without isolation.

Prasad and co-workers at Novartis have implemented the LAH reduction of acid **95** to alcohol **96**, a compound that was developed to understand the pharmacology of single S1P-receptors in the area of organ transplantation and autoimmunity (Scheme 23).[76a] A solution of amino acid HCl salt

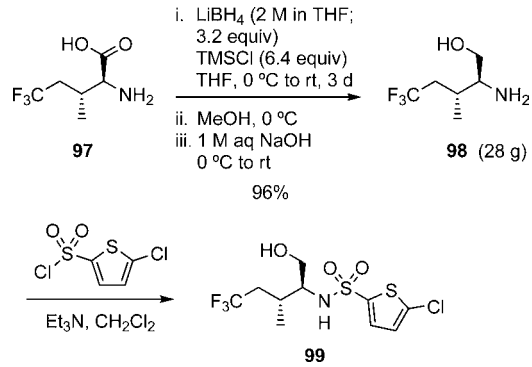
Scheme 23. LAH reduction of amino acid 95 to amino alcohol 96



95 in THF was slowly dosed with LAH (1 M in THF) at 5 °C, and the resulting mixture was heated to 56 °C for 4−5 h. After cooling to 0 °C, the reaction was quenched according to the Fieser procedure[34] to remove aluminum salts by filtration. Alcohol **96** was isolated by crystallization from heptane/EtOAc in 79% yield.

Wang and Resnick at Wyeth have reported the preparation of drug candidate **99**, a potent and selective γ-secretase inhibitor for the treatment of Alzheimer's disease, via the reduction of amino acid **97** to alcohol **98** (Scheme 24).[77] The reduction

Scheme 24. $LiBH_4$ reduction of amino acid 97 to amino alcohol 98



of acid **97** was carried out with large excesses of both $LiBH_4$ (2 M in THF, 3.2 equiv) and TMSCl (6.4 equiv) in THF at rt over 3 days. After quenching sequentially with MeOH and 1 M aqueous NaOH at 0 °C, the product was extracted into $CHCl_3$ and concentrated to afford alcohol **98** in 96% yield as an oil that was used in the next step without further purification.

5. ESTER REDUCTION

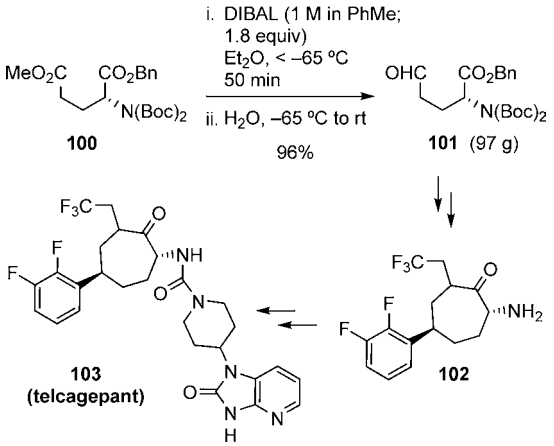
5.1. Acyclic Ester Reduction to Aldehyde. Very few examples of the large-scale reduction of acyclic esters to aldehydes exist in the literature, most likely due to difficulties avoiding over-reduction to the alcohol. Typically, esters are converted to aldehydes on large scale over two steps via reduction to the alcohol followed by oxidation. However, DIBAL[78] and Red-ALP-KTB (sodium methoxyethoxyaluminum hydride/pyrrolidine/KO*t*-Bu)[79]

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

have been successfully incorporated into processes for ester reductions to aldehyde products.

Burgey and co-workers at Merck have reported the preparation of cycloheptanone **102**, a key intermediate en route to telcagepant (**103**), a calcitonin gene-related peptide receptor antagonist for the treatment of migraine (Scheme 25).[78a]

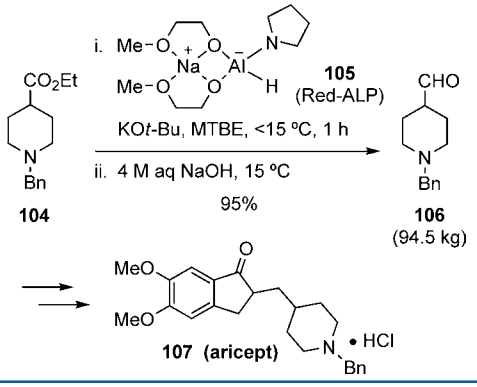
Scheme 25. DIBAL reduction of methyl ester 100 to aldehyde 101 en route to telcagepant (103)



In their synthesis, the methyl ester of **100** was chemoselectively reduced in the presence of a benzyl ester with a 1 M solution of DIBAL in toluene at −65 °C. Upon reaction completion, the cold mixture was quenched with water and warmed to room temperature. Following an extractive workup, crude aldehyde **101** was obtained in 96% yield and used in the next step without any further purification. Before further scale-up of this protocol, the highly flammable and peroxide-forming Et_2O would likely be replaced with another solvent to avoid the process safety risks associated with diethyl ether.

Abe and co-workers at Eisai in Japan have described the pilot-plant-scale reduction of ester **104** to *N*-benzyl-4-formylpiperidine (**106**), an intermediate in the synthesis of selective inhibitor of acetylcholinesterase aricept (**107**) for the treatment of Alzheimer's disease (Scheme 26).[79] Although reductions of

Scheme 26. Red-ALP-KTB reduction of ester 104 to aldehyde 106 en route to aricept (107)



ester **104** to aldehyde **106** could be carried out with DIBAL, cryogenic temperatures were required (not amenable for large-scale production), and a search for more practical conditions was undertaken. After substantial optimization of reaction conditions with respect to amine base, alkoxide base, solvent, and temperature, a mixture of complex sodium bis(2-methoxyethoxy)aluminum hydride/pyrrolidine (Red-ALP complex **105**) and KO*t*-Bu was identified as a highly selective reducing reagent (Red-ALP-KTB) that allowed for reduction close to ambient temperature and provided aldehyde **106** in high yield with minimal over-reduction to alcohol. After a basic quench and aqueous workup to remove aluminum salts, the crude aldehyde **106** was obtained in 95% yield. This material was purified further by distillation at reduced pressure to provide **106** as a colorless oil.

5.2. Acyclic Ester Reduction to Alcohol. Several methods have been described for the reduction of acyclic esters to alcohols on large scale. A survey of the process literature reveals LAH as the most common reagent for this transformation, typically in solvents such as THF, 2-MeTHF, and toluene.[80] Aqueous quenches of large-scale LAH reductions may involve acidic (H_2SO_4, HCl) or basic (K_2CO_3)[80h] conditions, or the Fieser workup.[34] Ethyl acetate[80i] has been used to destroy excess reagent prior to aqueous quench.

DIBAL will reduce esters to alcohols on large scale via the aldehyde intermediate.[11h,67c,81] Typical solvents for DIBAL reduction include CH_2Cl_2, toluene, THF, and mixtures thereof. An aqueous Rochelle salt or acidic quench follows reaction completion.

$NaBH_4$, either by itself[82] or in combination with other reagents (AcOH with simultaneous lactam reduction),[83] $CaCl_2$ (in situ synthesis of $Ca(BH_4)_2$),[84] $Na(OAc)_3BH$ (catalytic; methyl ester reduction in the presence of *tert*-butyl ester),[85] and $ZnCl_2$ (with concomitant aryl nitrile reduction to amine)[86]) have been employed on process scale for ester reduction to the alcohol. Heating is often required since esters are less reactive than aldehydes or ketones. Preferred solvents for $NaBH_4$ reductions include alcohols (MeOH, EtOH), THF, and 2-MeTHF, but examples in NMP[84b] and DME[86] also exist. After reaction completion, aqueous acidic or basic quenches consume residual borohydride. Alternatively, acetone can be added to consume excess $NaBH_4$ prior to the aqueous quench.

Other reagents such as $BH_3{\cdot}SMe_2$ (stoichiometric)/$NaBH_4$ (catalytic),[87] $Zn(BH_4)_2$ (prepared in situ from $LiBH_4$ and $ZnCl_2$),[88,89] borane (prepared in situ from $LiBH_4$ and $BF_3{\cdot}THF$),[90] $LiBH_4$[76a,91] (reactivity between LAH and $NaBH_4$; either commercial or prepared in situ from $NaBH_4$ and LiBr,[91d,91]), and Red-Al (Vitride, sodium bis(2-methoxyethoxy) aluminum hydride; 65−70 wt% in PhMe)[92] have also been employed.

Alternatively, $LiEt_3BH$ (Super-Hydride, 1 M solution in THF) is an unreported but potential reagent for the large-scale reduction of esters to alcohols, although the cost of this reagent may be a limiting factor, especially in late-development operations.

Ayers and co-workers at Aventis have described the large-scale reduction of methyl ester **110** to alcohol **111** for the synthesis of indazole **112**, a candidate for the treatment of psychiatric disorders (Scheme 27).[80g] Piperazine **108** underwent reaction with triflate **109** to afford methyl ester **110**, which was carried forward as a toluene solution into subsequent ester reduction. A solution of LAH·2THF (1 M in toluene), prepared by adding THF (2 equiv with respect to LAH) to a slurry of LAH in toluene at 5−15 °C, was held at 0 °C while adding the solution of **110**. The resulting mixture was warmed to 20 °C and, after reaction completion, recooled to 0 °C for water quench. After aqueous workup, the aluminum salts were removed by filtration, and the filtrate was concentrated to 4.03 kg of alcohol **111** as an amber oil.

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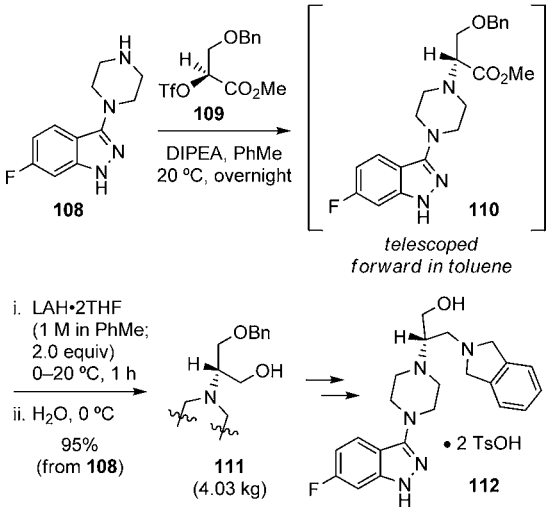
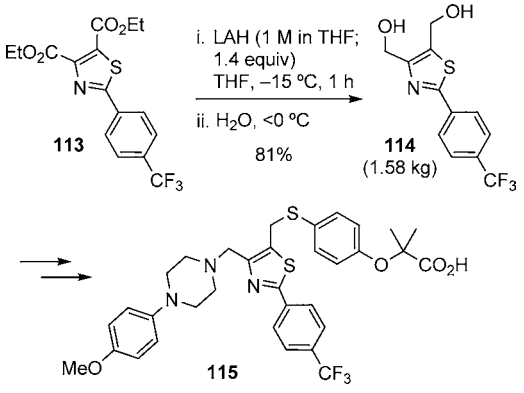
Scheme 27. LAH·2THF reduction of methyl ester 110 en route to 112



Guo and co-workers at GlaxoSmithKline reduced diester **113** to diol **114** for the preparation of thiazole **115**, a potent PPARpan agonist for the treatment of metabolic diseases (Scheme 28).[80e] A solution of **113** in THF was added to cooled

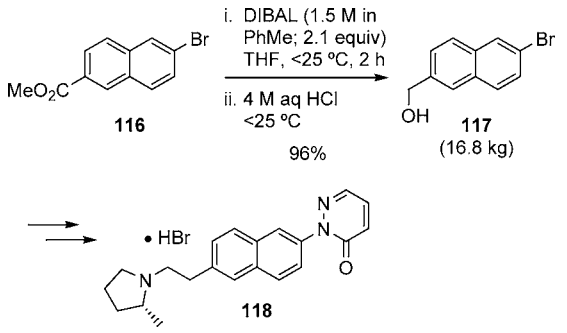
Scheme 28. LAH reduction of diester 113 to diol 114



LAH (1 M in THF) at such a rate to maintain a batch temperature between −15 and −10 °C, and the resulting mixture was held at −15 °C for 1 h. Low temperature was required to suppress mono- and bis-desfluoro byproducts. Upon reaction completion, the mixture was quenched with water and treated with aqueous H_2SO_4. Following an extractive workup with EtOAc, 1.58 kg of diol **114** were isolated via crystallization from *i*-PrOAc/CH_2Cl_2 in 81% yield.

Pu and co-workers at Abbott employed a large-scale ester reduction in their multikilogram synthesis of selective histamine H_3 antagonist **118**, a treatment for CNS conditions such as cognitive and memory disorders (Scheme 29).[67c] Initial LAH reduction of methyl ester **116** to alcohol **117** led to substantial desbromo byproduct (up to 20%). Several reductants were screened (DIBAL, $NaBH_4$, $LiBH_4$), and DIBAL was chosen as the best reagent for effecting ester reduction while suppressing debromination (<1% desbromo impurity). The conversion of **116** to **117** proceeded faster in noncoordinating solvents (toluene, CH_2Cl_2) than in THF or DME, and a combination of toluene/THF was chosen to circumvent the environmental concerns surrounding chlorinated solvents. Thus, a solution of

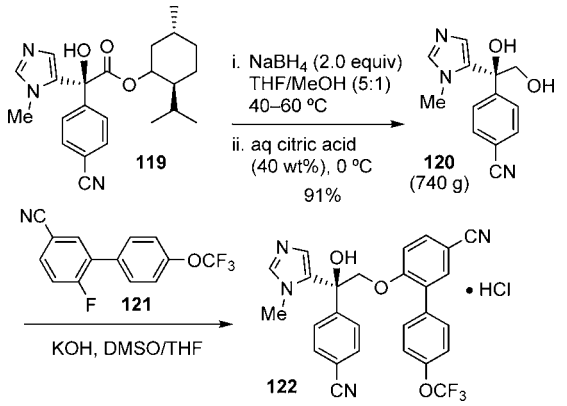
Scheme 29. DIBAL reduction of methyl ester 116 to benzylic alcohol 117



ester **116** in THF was charged with DIBAL (1.5 M in toluene) at a rate to maintain an internal temperature below 25 °C. Once the reaction was complete, the mixture was quenched with aqueous HCl, and following a series of aqueous washes and concentration of the organic phase, alcohol **117** was crystallized from heptane/toluene in excellent yield (96%) and purity (>99%).

Rozema and co-workers at Abbott Laboratories have published the preparation of biaryl **122**, a novel farnesyl transferase inhibitor for the treatment of cancer (Scheme 30).[82e]

Scheme 30. $NaBH_4$ reduction of (−)-menthol ester 119 to diol 120



The penultimate step of the synthesis involved the $NaBH_4$ reduction of (−)-menthol ester **119** to diol **120**. A mixture of **119** and $NaBH_4$ in THF was dosed with MeOH in three portions over 30 min to minimize the resulting exotherm (6–7 °C). The mixture was heated between 40–60 °C until <0.1% remaining **119**, cooled below 30 °C, and slowly quenched with 40% aqueous citric acid while maintaining the temperature below 40 °C. The quench required careful monitoring to mediate the large exotherm and considerable gas evolution (i.e., frothing and foaming). After aqueous workup and crystallization, diol **120** was isolated in 91% yield. These conditions did not reduce the cyano group, unlike stronger reducing agents such as $NaBH_4$/AcOH or $LiBH_4$.

Kato and co-workers at Chugai Pharmaceutical Company in Japan have applied a $Ca(BH_4)_2$-mediated reduction of ester **123** for the synthesis of fumarate salt **125**, a novel Ca^{2+} antagonist with potent cardioprotective activity (Scheme 31).[84c] Attempts to reduce the carboxylic acid precursor to **123** (not shown) via $LiBH_4$ reduction of the mixed anhydride (from $ClCO_2Et$) afforded alcohol **124** with partial racemization due to the

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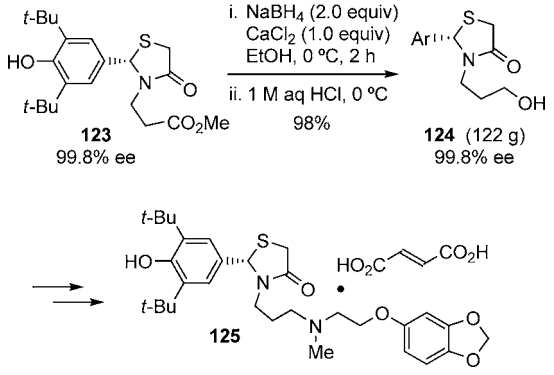
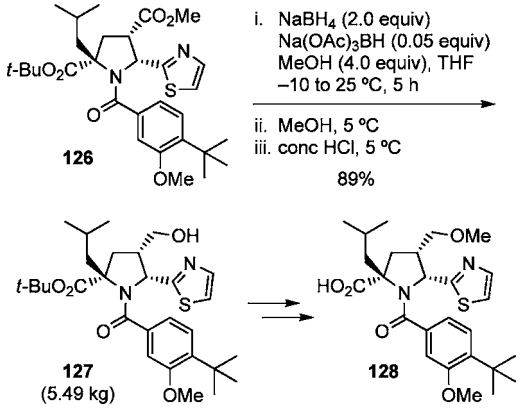
Scheme 31. Ester 123 reduction to alcohol 124 with $NaBH_4$/$CaCl_2$



basicity of the reductant. Alternatively, treating the methyl ester with $NaBH_4$ and $CaCl_2$ (in situ generation of $Ca(BH_4)_2$) in EtOH at 0 °C afforded **124** in excellent yield without any epimerization.

Slater, Xie, and co-workers at GlaxoSmithKline have reported the chemoselective reduction of a methyl ester in the presence of both a *tert*-butyl ester and an amide for the synthesis of hepatitis C virus polymerase inhibitor **128** (Scheme 32).[85]

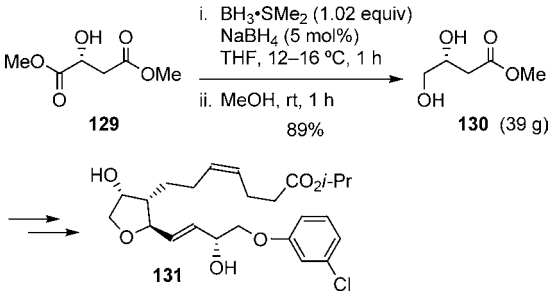
Scheme 32. Chemoselective methyl ester 126 reduction with $NaBH_4$ and catalytic $Na(OAc)_3BH$



The chemoselective reduction of the methyl ester **126** to alcohol **127** proved difficult and required an extensive screening of reagents to avoid side reductions of the *tert*-butyl ester and amide, and to suppress epimerization at the methyl ester stereocenter of the pyrrolidine ring. Reagents such as DIBAL, $LiBH_4$, $LiEt_3BH$ (Super-Hydride), and $NaBH_4$ led to over-reduction and epimerization on multigram scale. LAH performed well in small-scale pilots within a narrow range of low temperatures, but substantial amide reduction was observed on 100-g scale. Ultimately, a very specific set of conditions was found for the production of **127** that called for $NaBH_4$/MeOH in a 1:2 molar ratio and catalytic $Na(OAc)_3BH$ (2.5 mol% with respect to $NaBH_4$) in THF. The researchers rationalized this result by suggesting that $NaBH_4$ is converted to $NaB(OMe)_{4-n}H_n$ (n = 1−3) in the presence of $Na(OAc)_3BH$. Unlike commercial $NaB(OMe)_3H$, which caused extensive epimerization at C4, the $NaB(OMe)_{4-n}H_n$ prepared in situ maintained the chiral integrity of the molecule, perhaps due to lower basicity and higher reactivity. On kilogram scale, the reduction was carried out by adding MeOH to a cold (−10 °C) mixture of ester **126**, $NaBH_4$, and $Na(OAc)_3BH$ over 1 h and then stirring at 25 °C for 5 h. The reaction was quenched sequentially with MeOH and concentrated HCl, and after an aqueous workup, alcohol **127** was crystallized from MeCN in 89% yield.

Fox and co-workers at Dowpharma have published the synthesis of 11-oxa prostaglandin analogue **131**, a drug candidate for the reduction of intraocular pressure in the treatment of glaucoma (Scheme 33).[87] The first step of the

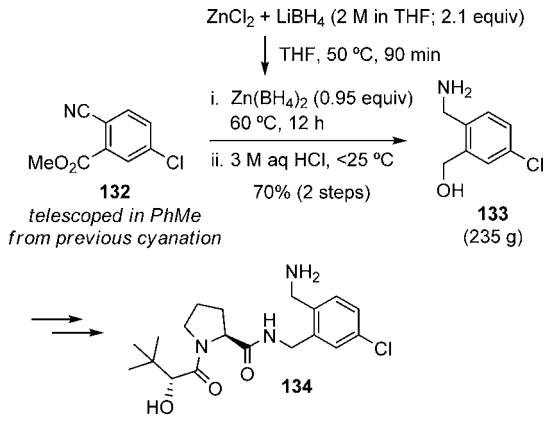
Scheme 33. Chemoselective BH_3·SMe_2 reduction of α-hydroxy ester 129 to diol 130 with catalytic $NaBH_4$



synthesis involved the chemoselective reduction of dimethyl D-malate (**129**) at the methyl ester adjacent to the hydroxyl group. To accomplish this reduction, neat BH_3·SMe_2 was added to a THF solution of **129** at 12−16 °C followed by the addition of $NaBH_4$ (5 mol%) in five portions. The role of $NaBH_4$ was to increase the reaction rate, since ester reduction with BH_3·SMe_2 was very slow. After reaction completion, the mixture was quenched with MeOH, and diol **130** was obtained in 89% yield following chromatography.

Nelson and co-workers at Merck have described the $Zn(BH_4)_2$ reduction of **132** en route to potent thrombin inhibitor **134**, a drug candidate for the regulation of a number of cardiovascular diseases (Scheme 34).[88] After a Rosenmund−

Scheme 34. Ester 132 reduction with $Zn(BH_4)_2$ generated in situ



von Braun reaction to install the cyano group of **132**, attempts to reduce the cyano ester to amino alcohol **133** were unsuccessful using various reductants (LAH, BH_3·SMe_2, $NaBH_4$, DIBAL). On the other hand, $Zn(BH_4)_2$, prepared in situ by treating $ZnCl_2$ with 2.1 equiv of $LiBH_4$ (2 M in THF) at 50 °C for 90 min, afforded amino alcohol **133** with minimal byproduct formation. A toluene solution of cyano ester was

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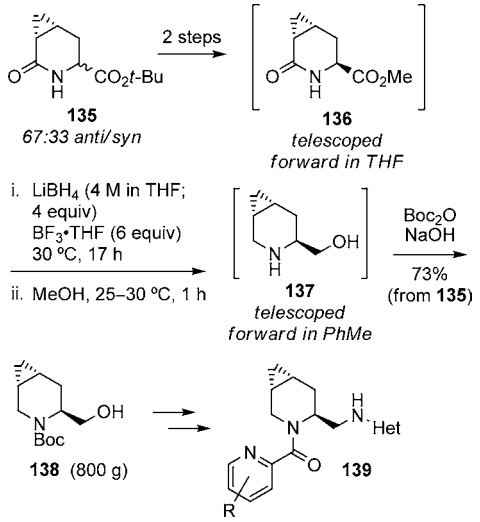
added to the freshly prepared solution of $Zn(BH_4)_2$ while the internal temperature was held below 65 °C. The ester was reduced faster than the nitrile, and these conditions gave complete conversion to **133** after 12 h. Following aqueous HCl quench and workup, the amino alcohol was crystallized from a heptane/toluene mixture in 70% yield.

Maton and co-workers at GlaxoSmithKline in Italy reported a dual ester/amide reduction for the preparation of Boc-protected piperidine **138**, a key intermediate to orexin antagonists **139** for the treatment of sleep disorders (Scheme 35).[90]

Scheme 35. Ester and lactam reduction with $LiBH_4$ to generate hydroxypiperidine 137

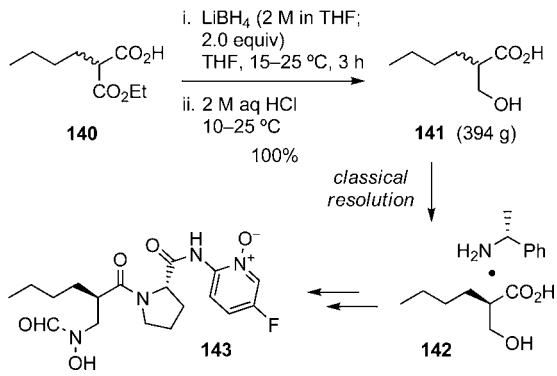


Amido ester **136** was obtained with high diastereomeric excess in two steps from *tert*-butyl ester **135**. Borane was the reagent of choice for the dual ester/lactam reduction of **136**. Originally, the reaction was effected by adding a THF solution of precomplexed **136** and BF_3·THF to $NaBH_4$ to generate BH_3 in situ. This protocol worked well on small scale, but only partial lactam reduction was observed on larger scale, a result attributed to the heterogeneity of the reaction mixture. More reproducible results on any scale were obtained when powdered $NaBH_4$ was replaced with $LiBH_4$ (4 M in THF). After reduction and MeOH quench, aqueous workup provided the crude hydroxypiperidine **137** as a toluene solution which was carried into subsequent amine protection. *N*-Boc **138** was obtained in 73% yield from *tert*-butyl ester **135** on multi-hundred-gram scale.

Prashad and co-workers at Novartis have described the preparation of (*R*)-2-butyl-3-hydroxypropionic acid (**142**), a key intermediate in the synthesis of drug candidate **143** (Scheme 36).[91d] The racemic precursor **141** was accessed via reduction of 2-butylpropanedioic acid monoethyl ester (**140**), and several conditions were evaluated for ester reduction. $NaBH_4$ in aqueous THF provided more than 10% of the diacid, whereas $LiBH_4$ in water did not promote good conversion to **141**. However, upon switching the solvent from water to THF, $LiBH_4$ provided the racemic hydroxy acid in quantitative yield after aqueous HCl quench and workup. Racemate **141** was resolved to **142** via classical resolution with (*R*)-α-methylbenzylamine.

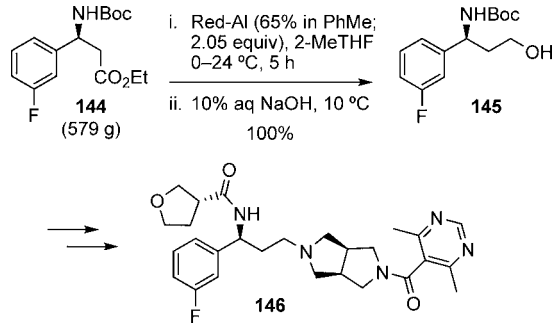
Huang, Cooper, and co-workers at Roche Palo Alto have incorporated a large-scale ester reduction into their synthesis of

Scheme 36. Selective ester reduction with $LiBH_4$ en route to 143



146, a potent CCR5 receptor antagonist for the treatment of HIV (Scheme 37).[92b] Originally, the direct reduction of ethyl

Scheme 37. Red-Al reduction of ethyl ester 144 to alcohol 145



ester **144** to the corresponding aldehyde (not shown) was attempted with DIBAL, but up to 13% over-reduction byproduct (**145**) was obtained even at −78 °C. Therefore, the aldehyde was prepared in a two-step sequence of ester reduction to alcohol followed by Swern oxidation. Several reducing agents were evaluated for the reduction of ester **144** to alcohol **145**. $NaBH_4$ in EtOH at reflux gave inconsistent results, whereas LAH provided **145** in almost quantitative yield. Red-Al also gave very clean alcohol and was the reagent of choice since it is commercially available as a toluene solution (65 wt%) and is less hazardous than LAH on scale. The reaction was performed on process scale by adding Red-Al to a cooled solution of ester in 2-MeTHF (0−15 °C). After warming to 24 °C and stirring for 5 h, the reaction was quenched with aqueous NaOH. Following an extractive workup, crude alcohol **145** was obtained as a viscous oil with 97% purity. One concern using Red-Al is the purging of 2-methoxyethanol, but this byproduct can be easily removed in the aqueous washes due to its high solubility in water.

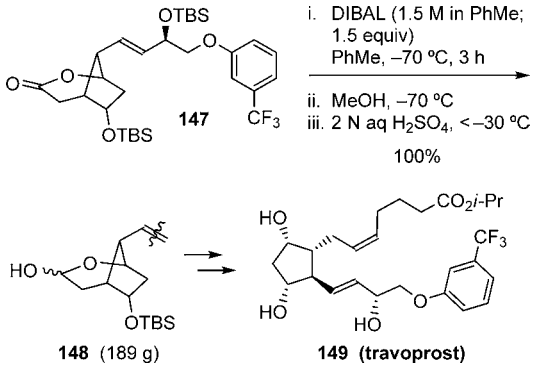
5.3. Lactone Reduction to Lactol. The reduction of lactones to the corresponding lactol is a more general practice in the process literature than the analogous reduction of acyclic esters to aldehydes. Lactone reduction to lactol is especially important in the area of saccharides. DIBAL is the preferred reagent for this transformation,[68d,93] which is typically performed in toluene or CH_2Cl_2 at temperatures between −78 and −20 °C. Commercially available DIBAL solutions (in toluene, hexanes, cyclohexane, heptane, THF, CH_2Cl_2) are convenient sources of the reagent for large-scale operations. These reductions are

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

usually quenched at low temperature with aqueous Rochelle salt, dilute acid (HCl, H_2SO_4), MeOH, or EtOAc.[93d] Other reagents used for the reduction of lactones to lactols on large scale include KBH_4 (less hygroscopic than $NaBH_4$ and easier to handle in plant) in combination with $CaCl_2$ (in situ generation of $Ca(BH_4)_2$),[94] Li(*s*-Bu)$_3$BH,[42i] LiB(O*t*-Bu)$_3$H,[95] and poly(methylhydrosiloxane) in the presence of catalytic Cp_2TiF_2.[96]

Researchers at Chirotech Technology have prepared lactol **148** as an intermediate to travoprost (**149**), a candidate for the treatment of glaucoma and ocular hypertension (Scheme 38).[93e]

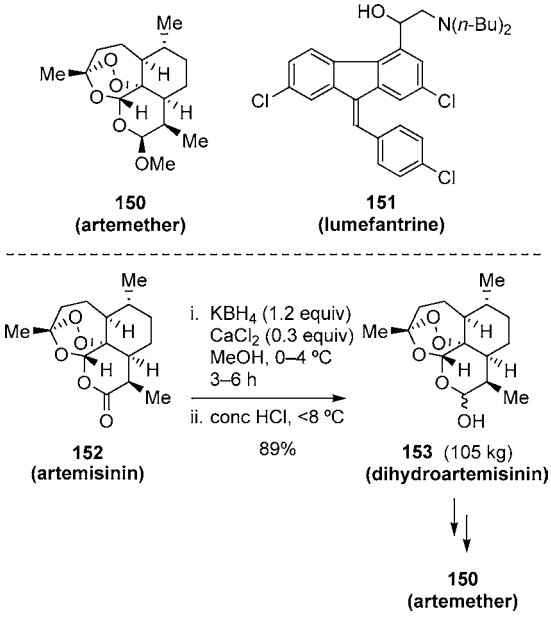
Scheme 38. DIBAL reduction of lactone 147 to lactol 148



Lactol **148** was prepared via reduction of lactone **147** with DIBAL (1.5 M in PhMe) under cryogenic conditions (−70 °C), and the mixture was quenched with MeOH and aqueous H_2SO_4 while maintaining a batch temperature below −30 °C. The crude lactol was extracted into MTBE and concentrated to a colorless oil in quantitative yield for use in subsequent Wittig olefination.

Fuenfschilling and co-workers at Novartis Pharma AG in Switzerland have reported a lactone reduction on >100-kg scale for the production of antimalaria drug coartem, which is composed of two active ingredients: artemether (**150**) and lumefantrine (**151**) (Scheme 39).[94] During the synthesis of

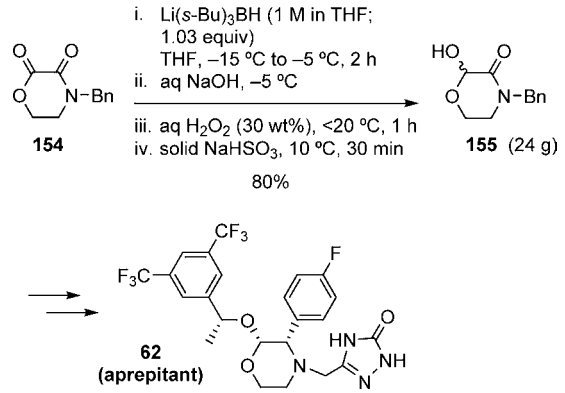
Scheme 39. Lactone 152 reduction to lactol 153 mediated by $KBH_4/CaCl_2$



artemether, the lactone moiety of natural product artemisinin (**152**) was reduced to dihydroartemisinin (**153**) by adding solid KBH_4 portionwise to a suspension of **152** and $CaCl_2$ in MeOH. This protocol successfully provided 19 batches of **153** in the plant with yields in the 74−84% range; however, subsequent batches showed less consistent and diminishing yields until batch #35 provided **153** in only 2% yield. A thorough investigation found that neither human error, stirring mode, the addition of Fe salts (iron catalyzes the cleavage of the peroxy group in artemether, and this is the mechanism of action of the drug in vivo), nor moisture (5% yield loss) accounted for this dramatic decrease in yield. Large drops in yield were observed when the reaction was quenched with concentrated HCl at 20 °C instead of at 0−6 °C (40% drop) or when the amount of concentrated HCl during the workup was increased from 1.5 to 2.3 equiv (25% drop). However, these factors could not account for the complete failure of batch #35. After further investigation, it was discovered that contaminant KOH in the KBH_4 proved to be the biggest contributor to poor yields, and reductions in the presence of 1 mol% KOH provided **153** in <10% isolated yield. On the basis of these findings, the process was optimized to improve robustness by using KBH_4 with low KOH content, adding KBH_4 within 6 h to prevent the base-catalyzed decomposition of artemisinin, reducing the reduction temperature to 0−4 °C, and adjusting to pH 4−6 during quench. These optimizations led to a robust method that provided dihydroartemisinin (**153**) with an average yield of 89%, and required less KBH_4 (1.2 equiv) due to its slower rate of decomposition at lower temperatures.

Brands and co-workers at Merck effected the chemoselective reduction of lactone **154** to lactol **155** as part of their convergent synthesis of NK_1 receptor aprepitant (**62**), a treatment for chemotherapy-induced emesis, depression, and other indications (Scheme 40).[42i] Treatment of **154** with Li(*s*-Bu)$_3$BH

Scheme 40. Lactone 154 reduction with Li(*s*-Bu)$_3$BH en route to aprepitant (62)

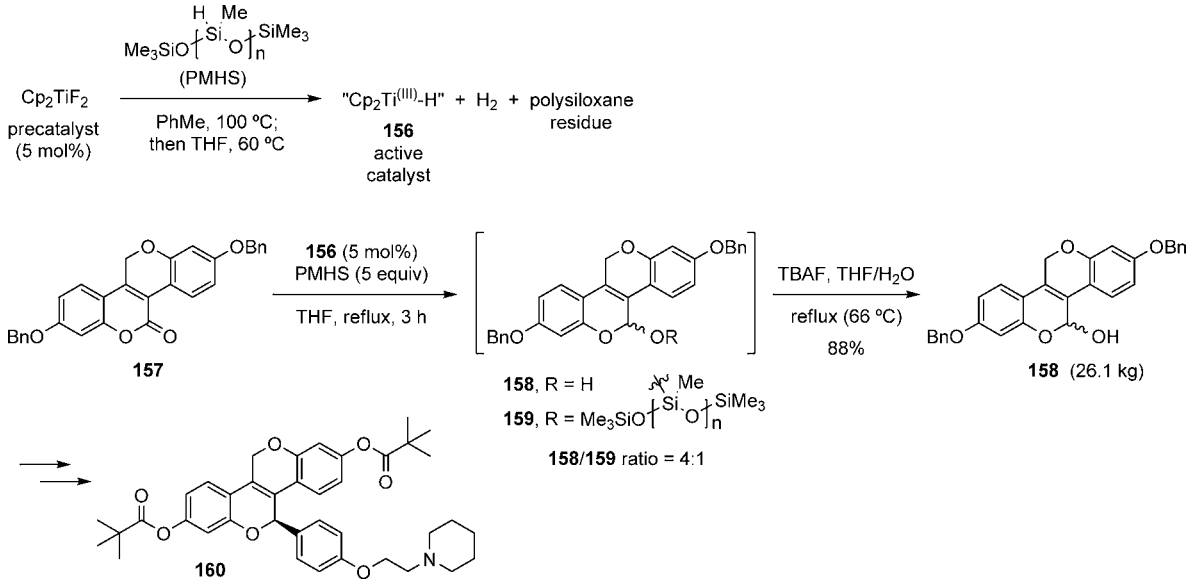


(L-Selectride; 1 M in THF) at −15 °C selectively reduced the lactone moiety in the presence of the lactam. After reaction completion, the mixture was quenched with sequential additions of 5 M aqueous NaOH, 30 wt% aqueous H_2O_2 (very exothermic), and solid $NaHSO_3$. Following extractive workup and a series of crystallizations, lactol **155** was isolated in 80% yield.

Depré and co-workers at Johnson & Johnson have described the preparation of lactol **158** en route to **160**, a selective estrogen receptor modulator for the treatment of hot flashes and vaginal dryness (Scheme 41).[96] Initially, lactone **157** reduction

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

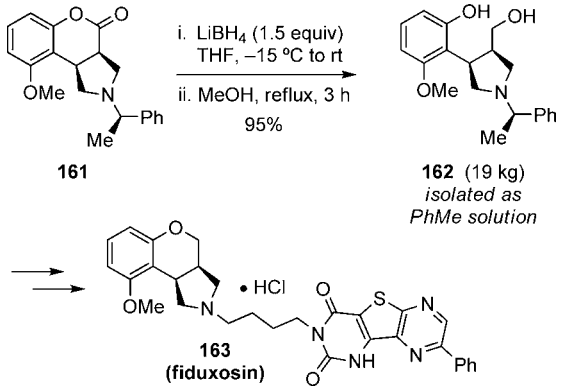
Scheme 41. PMHS/Cp_2TiF_2-mediated reduction of lactone 157 to lactol 158



to lactol **158** was implemented with DIBAL in CH_2Cl_2, but it was necessary to control the amount of reductant to avoid over-reduction to the diol or saturated ether. In addition, large amounts of waste were generated (60−90 kg of waste per kg of lactol **158**). Other reduction methods were tested (Red-Al, $Et_3SiH/Ru_3(CO)_{12}$ (catalytic), $PhSiH_3/Ru_3(CO)_{12}$ (catalytic), poly(methylhydrosiloxane) (PMHS)/$Ru_3(CO)_{12}$, PMHS/Et_2Zn-eda, $PhSiH_3/Cp_2TiF_2$ (catalytic), and PMHS/Cp_2TiF_2), but only the last two combinations gave acceptable results. Since PMHS is a cheaper reagent than $PhSiH_3$ and provided lactol with higher purity, it became the reagent of choice. The active catalyst was generated by treating a suspension of the precatalyst Cp_2TiF_2 (5 mol%) in toluene at 100 °C with a toluene solution of PHMS (2 equiv with respect to Cp_2TiF_2). These conditions avoided the induction period observed at lower temperature which gave rise to a 5 °C exotherm and sudden pressure buildup in the reactor. After catalyst activation, the mixture was cooled to 60 °C, and THF was added. The resulting dark-blue solution of active catalyst **156** was then added to a suspension of lactone **157** and PHMS (5 equiv) at 55−60 °C, and the reaction mixture was stirred at 50−55 °C for 3 h to give a mixture of lactol **158** and silyl acetal **159** in 4:1 ratio. The complete hydrolysis of the silyl acetal intermediate **159** to **158** was accomplished by slowly adding a solution of TBAF (1 M in THF) in water to keep the amount of hydrogen gas evolution (140 L/mol of lactone **157**) and ensuing foaming under control. The subsequent addition of Dicalite (diatomaceous earth) facilitated the removal of polysiloxane byproducts as an insoluble, hard powder via filtration. After concentration of the filtrates, the addition of EtOH caused the crystallization of lactol **158**, which was obtained in 88% yield on multikilogram scale.

5.4. Lactone Reduction to Diol. Lactone reduction to diol on large scale has rarely been reported in the mainstream literature. We found only one example, reported by Haight and co-workers at Abbott for the preparation of fiduxosin (**163**), a drug candidate for the treatment of benign prostatic hyperplasia (Scheme 42).[97] The lactone moiety in **161** was converted to the saturated ether in fiduxosin via a reduction/cyclization protocol. Thus, lactone reduction was effected by adding a slurry of **161** in THF to a solution of $LiBH_4$ in that same

Scheme 42. $LiBH_4$ reduction of lactone 161 to diol 162 en route to fiduxosin (163)



solvent at −15 °C. After warming to ambient temperature, the reaction was quenched with the addition of MeOH, followed by a 3-h reflux to destroy the boronate ester and eliminate residual boron as trimethyl borate. An aqueous, extractive workup produced diol **162** in 95% yield as a toluene solution. The researchers mentioned that this method was employed for the first scale-up of fiduxosin, but was later replaced with a $NaBH_4$ reduction that provided diol **162** in >95% yield and >98% purity.

6. AMIDE REDUCTION

6.1. Amide Reduction to Aldehyde. The process literature contains examples in which Weinreb amides are reduced to aldehydes via LAH,[80d,98] DIBAL,[11g,99] or Red-Al.[100] While morpholine amides offer reactivity comparable to that of Weinreb amides without the high-energy dimethylhydroxylamine, large-scale additions to morpholine amides typically involve carbon nucleophiles. We also found a single example in which an *N*-acyl sultam is reduced to aldehyde on large scale.[101]

Carey and co-workers at GlaxoSmithKline developed the reduction of Weinreb amide **164** as one of several synthetic approaches to aldehyde **165** (Scheme 43).[80d] Only 0.34 equiv of LAH was required to consume **164** in THF at −35 °C, and

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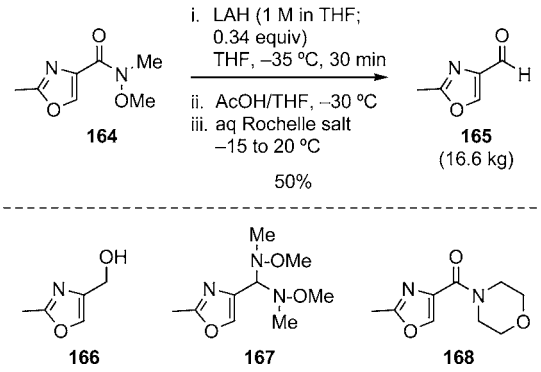
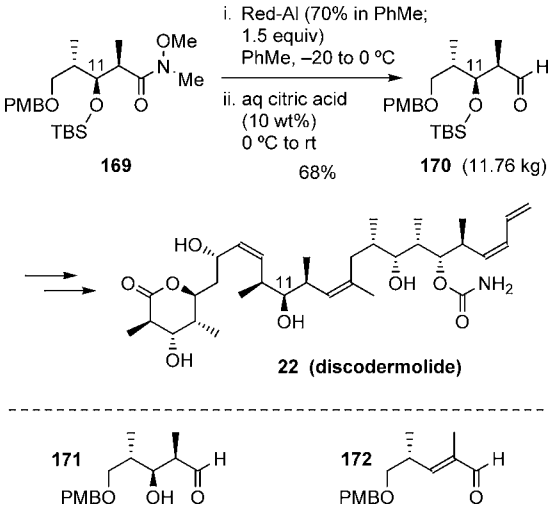
Scheme 43. LAH reduction of Weinreb amide 164



there was no evidence of over-reduction to alcohol **166** even with prolonged reaction times. The reaction mixture was quenched with AcOH and treated with aqueous Rochelle salt solution to dissolve the aluminum salts. The volume of AcOH quench was optimized to provide a pH 7 solution after subsequent potassium/sodium tartrate addition, which was key as aldehyde **165** decomposes under too strongly acidic or basic conditions. (Quenching with EtOH led to a pH 14 solution via LiOEt and degradation.) Sodium hydrogen sulfate washes were acidic enough to extract dimethylhydroxylamine (necessary to avoid the formation of aminal **167**) with only slight decomposition of aldehyde, and continued workup and crystallization from MTBE/heptane provided 16.6 kg of **165** as an off-white solid. Morpholine amide **168** was explored as an alternative to **164**, but similar reducing conditions provided lower yields of aldehyde and greater alcohol **166** byproduct.

Mickel and co-workers at Novartis reduced Weinreb amide **169** to aldehyde **170** using Red-Al conditions in the synthesis of discodermolide (**22**), a potent inhibitor of tumor cell growth (Scheme 44).[100] A previous synthesis by Smith reduced the

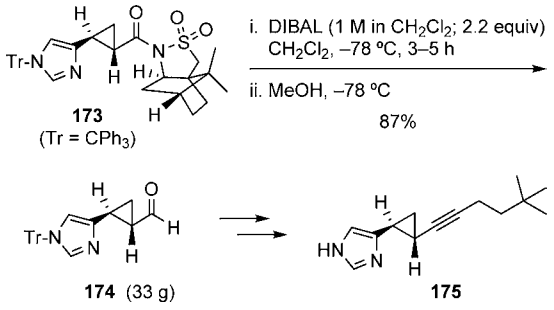
Scheme 44. Red-Al reduction of Weinreb amide 169 for the synthesis of discodermolide (22)



amide using DIBAL at −78 °C;[102] however, such cryogenic conditions are difficult to achieve on plant scale. Instead, a solution of amide **169** in toluene was dosed with Red-Al (70% in toluene) over 1 h while maintaining an internal temperature of −20 °C; after an additional hour the mixture was warmed to 0 °C and quenched with aqueous citric acid solution. Byproducts **171** from desilylation and **172** from β-elimination formed if the reaction mixture were held at 0 °C for too long prior to quench. After aqueous workup and chromatography, 11.76 kg of aldehyde **170** was isolated in 68% yield.

Liu and co-workers at Abbott cleaved the camphorsultam auxiliary of **173** to aldehyde **174**, an intermediate to the potent histamine H_3 antagonist **175** (Scheme 45).[101] A solution of

Scheme 45. Reduction of *N*-acyl sultam 173 to aldehyde 174

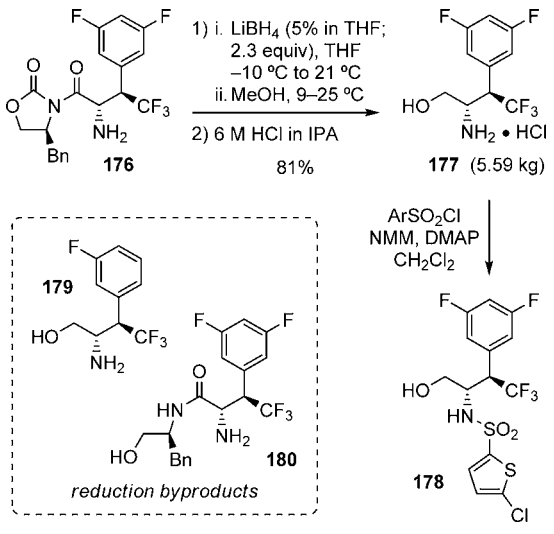


sultam in CH_2Cl_2 at −78 °C was dosed with DIBAL (1 M in CH_2Cl_2) dropwise over 30 min, stirred at −78 °C until reduction completion, and then quenched with methanol. The authors did not comment on possible over-reduction to the alcohol, and aldehyde **174** was obtained in high yield (87%) after aqueous workup and chromatography.

6.2. Amide Reduction to Alcohol. Reductions of amides to alcohols on process scale typically involve cleavage of a chiral auxiliary (e.g., *N*-acyl sultam,[103] *N*-acyl oxazolidinone[77,98b,104]). LAH^{103} has been used to reduce an *N*-acyl sultam, whereas $LiBH_4$[77,98b,104a] and $NaBH_4$[104b] are the choice reagents for reduction of *N*-acyl oxazolidinones. We also found an example of Gabriel amination in which the phthalimide is reduced to an amido alcohol via $NaBH_4$.[105]

In the penultimate synthetic step to **178**, Alimardanov and co-workers at Wyeth removed the Evans auxiliary from **176** using $LiBH_4$ (Scheme 46).[104a] Two impurities, **179** and **180**,

Scheme 46. Cleavage of Evans auxiliary from 176 using $LiBH_4$



were identified from this reduction. Desfluoro **179** was formed when adding **176** to a solution of $LiBH_4$, and this byproduct

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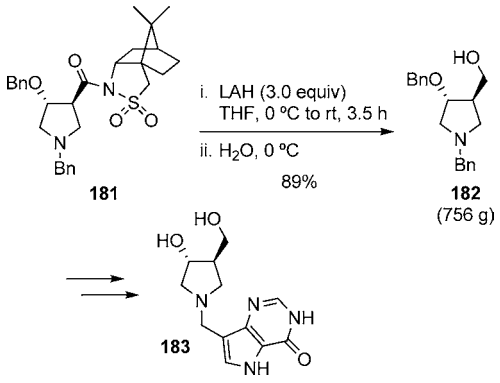
was easily suppressed by reversing the order of addition. Minimizing **180** was a greater challenge; its levels were controlled to 2−3% on multikilogram scale by maintaining the solution of **176** in THF at −10 to 0 °C while adding $LiBH_4$. The mixture was warmed to 21 °C, and upon reaction completion was quenched with MeOH addition while cooling between 9−25 °C. Aqueous workup and salt formation provided **177** in 81% overall yield.

Chand and co-workers at BioCryst Pharmaceuticals prepared chiral alcohol **182** as a core intermediate to purine nucleoside phosphorylase inhibitor **183** (Scheme 47).[103] A mixture of

Scheme 47. Reduction of *N*-acyl sultam 181 to alcohol 182

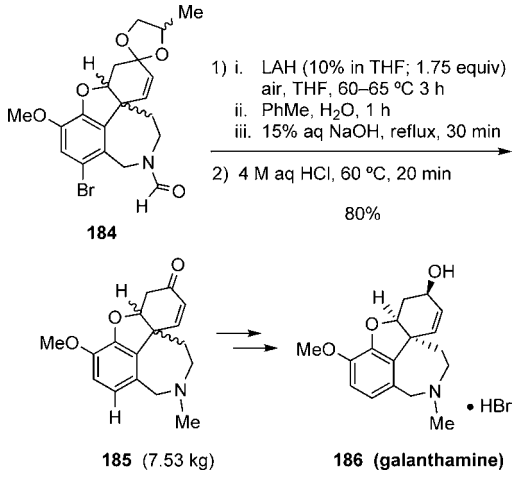


LAH in THF at 0 °C was dosed with a THF solution of sultam **181** in portions over 2 h and allowed to warm to room temperature. After reduction completion, the mixture was cooled at 0 °C and quenched with water. Aluminum salts were removed from the reaction mixture by filtration through Celite, and aqueous workup and concentration of the filtrate provided alcohol **182** as an oil which solidified on standing.

6.3. Amide Reduction to Saturated Amine. The most prevalent transformation for large-scale amide reduction is conversion to the saturated amine ($RCONR_2$ to RCH_2NR_2). A survey of the literature reveals LAH[11f,38,106] as the most common reagent for the carbonyl reduction of amide to amine, although aluminum hydrides may promote cleavage of the amide bond as a side reaction. Borane[47] is also commonly used for carbonyl reduction of amide to amine, and this reagent may be employed as commercial complexes (BH_3·THF,[91b,107] BH_3·SMe_2[108]) or more safely generated in situ from borohydride and BF_3[90,109] or H_2SO_4.[110] In addition, amides have been reduced to amines using DIBAL,[111] Red-Al (Vitride),[112] or sodium acyloxyborohydride (from $NaBH_4$ in AcOH).[83,113]

Fröhlich, Jordis, and co-workers at Sanochemia reduced a formyl group to a methyl group for the synthesis of galanthamine (**186**), a treatment for Alzheimer's disease (Scheme 48).[38] Formamide **184** in THF was treated with LAH solution (10% in THF) while bubbling air (20% oxygen, 80% nitrogen) through the mixture. Although air sparging was unnecessary on small scale (10−20 g **184**), its absence on larger scale resulted in negligible conversion to **185**. The dual reductions of amide and bromide produced an exotherm which raised the temperature to 60−65 °C without external heating. Quenching with water produced another exotherm with hydrogen gas evolution, and the initial charges of water transformed the mixture to an immobile gel which thinned with continued dilution. Aqueous NaOH solution was added after the water quench, and the resulting mixture was heated at reflux for 30 min. After hot

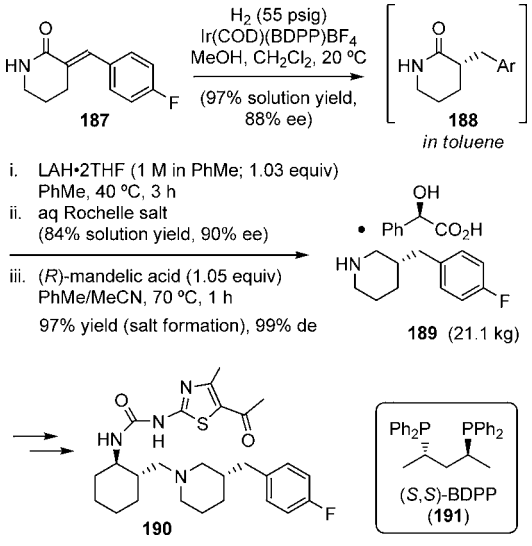
Scheme 48. LAH reduction of *N*-formyl 184 to *N*-methyl 185



filtration and workup, the reduction product was treated with aqueous acid to hydrolyze the ketal and then basified to provide 7.53 kg of freebase **185** as an off-white powder.

Yue and co-workers at Bristol-Myers Squibb telescoped an asymmetric hydrogenation and lactam reduction for their synthesis of CCR3 antagonist **190**, a potential inflammation suppressant for asthma and allergic rhinitis (Scheme 49).[106d]

Scheme 49. Conversion of lactam 188 to piperidine 189



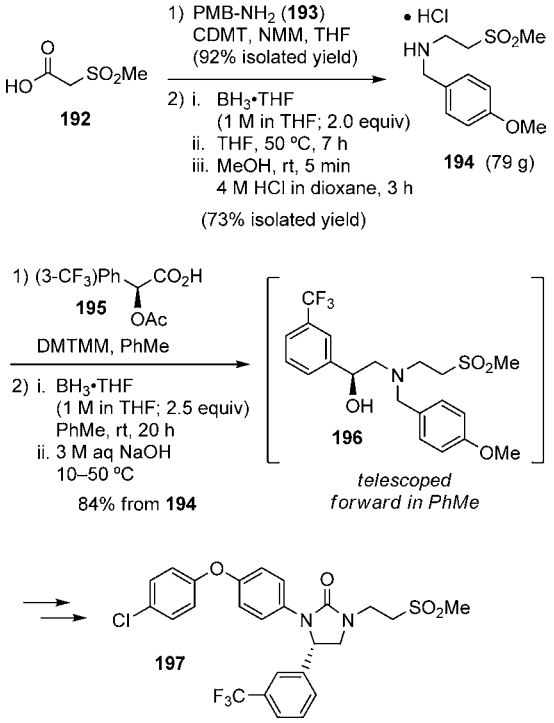
After an extensive catalyst screen for the asymmetric hydrogenation of α,β-unsaturated lactam **187**, the cationic Ir complex with (*S*,*S*)-BDPP (**191**) provided **188** with the best selectivity (90% ee) and low catalyst loading (0.2−1.0 mol%). The resulting solution of chiral lactam in toluene solution was telescoped into reduction by cooling to 10 °C, dosing with LAH·2THF (1 M in toluene), and heating at 40 °C for 3 h. As a result, **188** was reduced to the corresponding piperidine without racemization. The mixture was quenched with aqueous Rochelle salt solution, which offered the best phase separation and control of heat evolution. After classical resolution via (*R*)-mandelic acid with crystallization from toluene/MeCN, 21.1 kg of salt **189** were isolated with 99% de. This telescoped sequence was an improvement over an earlier approach that hydrogenated **187** using nonstereoselective conditions and,

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

after lactam reduction, lost half of the racemic piperidine to classical resolution.

Villhauer, Shieh, and co-workers at Novartis prepared tertiary amine **196** from a pair of amidation/reduction sequences for the synthesis of **197**, a cannabinoid-1 antagonist for the treatment of obesity and diabetes (Scheme 50).[107a] The CDMT

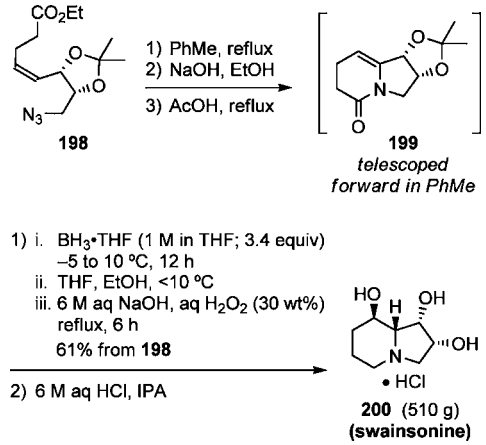
Scheme 50. Pair of amidation/reduction sequences to 196



coupling of acid **192** and *p*-methoxybenzylamine provided an amide (not shown) that was dissolved in THF and dosed with BH_3·THF (1 M in THF). The resulting mixture was heated at 50 °C until reduction completion and cooled to room temperature for MeOH quench. Treatment with 4 M HCl in dioxane followed by THF dilution provided the secondary amine HCl salt **194** as solids which were collected by filtration. Subsequent DMTMM coupling[114] of amine **194** with acid **195** provided a tertiary amide (not shown) which was charged in toluene with BH_3·THF (1 M in THF) and stirred at ambient temperature for 20 h. After complete conversion, the mixture was cooled at 10 °C and charged with aqueous NaOH in portions to minimize foaming and control the rate of exotherm. (Quenching increased the internal temperature to 50 °C.) Tertiary amine **196** was extracted into toluene in 84% yield and carried forward without further purification.

Sharma and co-workers at GLYCO Design employed BH_3·THF for a same-pot lactam reduction and olefin hydroboration in their synthesis of swainsonine (**200**), an α-mannosidase II inhibitor (Scheme 51).[107b] A solution of lactam **199** in toluene, prepared in a telescoped sequence from azide **198**, was slowly dosed with borane (1 M in THF) while maintaining an internal temperature below −5 °C. The resulting mixture was warmed to 10 °C over 12 h, and upon reaction completion the toluene was removed by vacuum distillation and replaced with THF. Ethanol was added while maintaining <10 °C, followed by aqueous solutions of 6 N aqueous NaOH and 30% aqueous H_2O_2. The quenched mixture was heated at reflux for 6 h, and then peroxides were reduced via

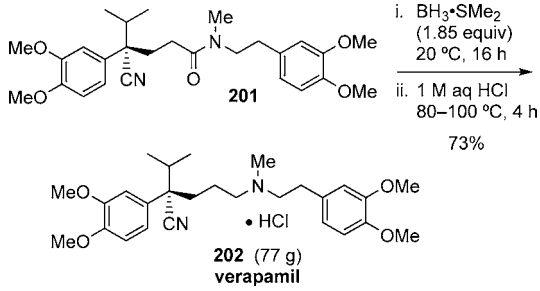
Scheme 51. Concurrent lactam reduction and olefin hydroboration of 199



$NaHSO_3$. Aqueous workup, crystallization, and salt formation provided **200** in 61% overall yield from **198**.

Brookes and co-workers at Celltech-Chiroscience employed BH_3·SMe_2 for an amide reduction to complete the synthesis of verapamil (**202**), a treatment for cardiovascular ailments (Scheme 52).[108] Both the reducing conditions and workup

Scheme 52. Synthesis of verapamil (202) via chemoselective amide reduction



required substantial optimization. Various reagents were unsuitable for the conversion of **201** to **202**. Aluminum hydrides tended to promote cleavage of the amide bond, whereas BH_3·THF had poor selectivity for amide versus nitrile reduction. Alternatively, BH_3·SMe_2 reduced the amide with minimal impact on the nitrile by charging the reagent at 0−5 °C and warming to room temperature. Forcing conditions were required to cleave the resulting **202**−borane complex, and the reaction mixture was quenched into a solution of 1 M aqueous HCl preheated to 80−85 °C. (More concentrated HCl solutions led to decomposition.) Once the transfer was complete, the mixture was heated at reflux (100 °C) for 4 h to fully sequester the borane and remove THF via distillation. In the absence of organic solvent, the HCl salt **202** oiled from the acidic solution upon cooling, and it was necessary to extract the API into CH_2Cl_2. After solvent swap, verapamil·HCl was crystallized from IPA/MTBE and collected on filter as a white powder. While this process was suitable for large laboratory scale or small plant scale, Brookes and coauthors cautioned that the special handling and costs associated with BH_3·SMe_2 would be significant disadvantages on larger scale.

Guercio and co-workers at GlaxoSmithKline developed the reduction of oxopiperazine **203** for the synthesis of NK-1 receptor antagonist **205** (Scheme 53).[109c] Initially, the amido

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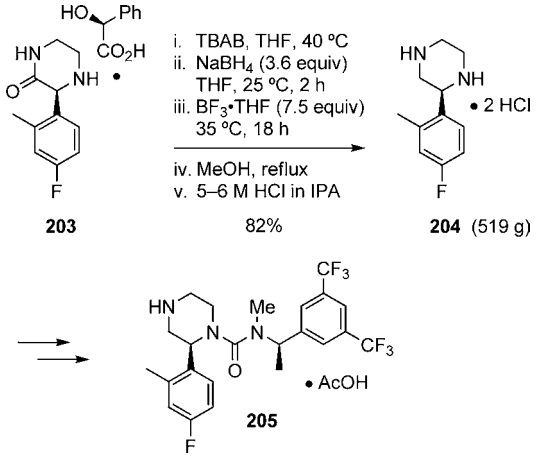
Scheme 53. Reduction of lactam 203 to piperazine 204



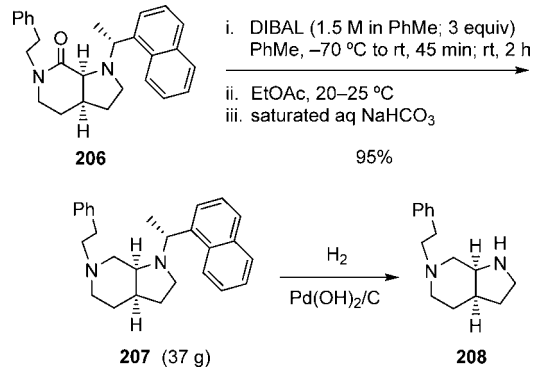
group of **203** was reduced on kilogram scale using the expensive and relatively unstable BH_3·THF complex.[48] Several alternative reduction conditions (LAH, Red-Al, sodium metal) provided only partial reduction and degradation while others ($NaBH_4$, $LiBH_4$, BH_3·SMe_2, $NaBH(OAc)_3$) gave negligible conversion to **204**. A design of experiment (DOE) around the in situ preparation of diborane from $NaBH_4$ and BF_3·OEt_2 revealed that low dilution and high temperature were both required for good conversion of freebased **203** to **204** in THF; however, heating the flammable diborane at 55 °C posed safety hazards and contributed to epimerization (in concert with residual NaOH from freebasing) during reduction on 80-kg scale. As an alternative to freebasing **203** prior to reduction, TBAB[115] was used to increase the solubility of the mandelic salt in THF (via increased solvent ionic character) for direct conversion to the piperazine. Further process refinements replaced BF_3·OEt_2 with BF_3·THF to avoid diethyl ether (low flash point) and replaced granular $NaBH_4$ with powder reagent to enhance conversion at lower temperatures. On 1-kg scale, a homogeneous solution of mandelic salt **203** and TBAB in THF was added to a suspension of $NaBH_4$ in THF at 25 °C and then dosed dropwise with BF_3·THF. The resulting mixture was held at 35 °C for at least 18 h, quenched with MeOH at 35 °C, and heated at reflux. The slurry was filtered and the filtrate treated with HCl (5−6 M in IPA) to provide the bis-HCl salt **204** in 82% yield with >99:1 er.

Shieh, Prasad, and co-workers at Novartis employed DIBAL for the lactam reduction of **206** en route to bicyclic amine **208**, a core intermediate for an antitumor compound (Scheme 54).[111b] A solution of **206** in toluene was cooled at −70 °C and dosed with DIBAL (1.5 M in toluene). The mixture was warmed to room temperature, stirred for 2 h, and quenched with ethyl acetate to consume unreacted DIBAL. A second quench with saturated aqueous $NaHCO_3$ precipitated the aluminum salts as granular solids which were easily separated by filtration. Concentration of the organic filtrate provided **207** as an oil that was further purified by silica gel chromatography to purge residual metal salts which might poison the catalyst in subsequent hydrogenation.

7. IMIDE REDUCTION

7.1. Imide Reduction to Saturated Amine. The reduction of imides at both carbonyls to the saturated amine is an extension of the amide-to-amine reductions highlighted in the preceding section. Reagents for this transformation on

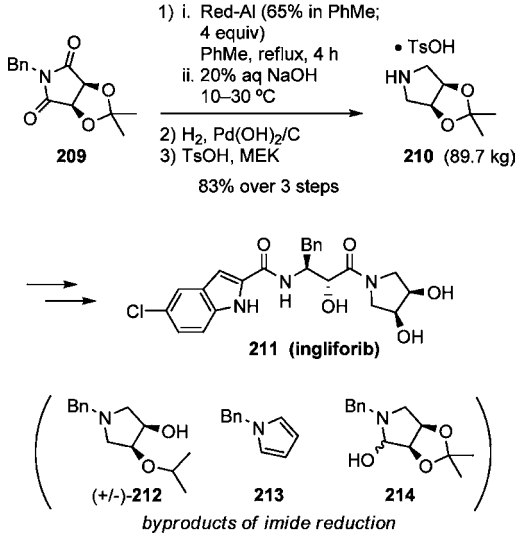
Scheme 54. DIBAL reduction of lactam 206



process scale include Red-Al,[92b,116] LAH,[80f,117] and borane complexes.[118] Reduction of the first imide carbonyl provides an intermediate *N*-acyl hemiaminal which often requires forcing conditions (high temperature, excess hydride reagent) for further reduction.[92b,116,118b,119]

Researchers at Pfizer and DSM Pharmaceutical Chemicals employed a DOE approach for the rapid development of a Red-Al reduction for the synthesis of ingliforib (**211**), a glycogen phosphorylase inhibitor for the treatment of diabetes (Scheme 55).[116] Imide **209** was previously reduced to pyrrolidine

Scheme 55. Red-Al reduction of imide 209 to pyrrolidine 210



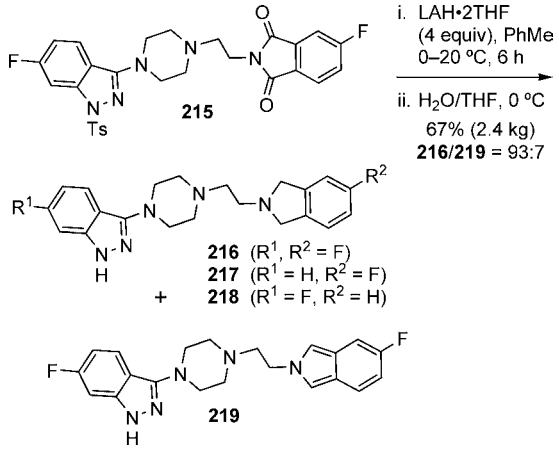
210 on kilogram scale using BH_3·THF;[118a] however, this relatively expensive reagent poses safety hazards,[48,120] and its Lewis acidity led to isopropyl ether **212** as a byproduct from competitive reduction of the ketal. Alternatively, non-Lewis acidic aluminates such as the inexpensive Red-Al are unreactive toward ketals, and pilot Red-Al reductions of imide to **210** did not generate isopropyl ether; however, switching to this reagent produced two new byproducts: pyrrole **213** (4−13%) and hemiaminal **214** (6−16%). Higher temperatures and longer reaction times led to increased pyrrole **213**, whereas the same higher temperatures and longer reaction times were required to convert hemiaminal **214** to desired pyrrolidine. Furthermore, the inverse addition of imide to a solution of Red-Al suppressed the pyrrole but increased the formation of hemiaminal. A screening DOE was employed to find the proper balance between temperature, duration, and reagent concentration.

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156−1184

Optimized conditions added imide **209** to Red-Al (4 equiv; both components in toluene) over 40 min at 20−35 °C, and heated at reflux for 4 h to generate the desired pyrrolidine with negligible pyrrole **213** and complete consumption of hemiaminal **214**. The solution was quenched with 20% aqueous NaOH while maintaining internal temperature of 10−30 °C, and the organic layer was separated, water-washed, and concentrated to a thin oil of pyrrolidine (93% yield, 99% GC purity). This oil was carried forward to subsequent hydrogenation and TsOH salt formation to provide 89.7 kg of **210** for an 83% overall yield.

Ayers and co-workers at Aventis prepared a series of isoindolines (e.g., **216**) for the treatment of psychiatric disorders via the reduction of phthalimides (e.g., **215**; Scheme 56).[80g]

Scheme 56. Reduction of phthalimide 215 using LAH·2THF

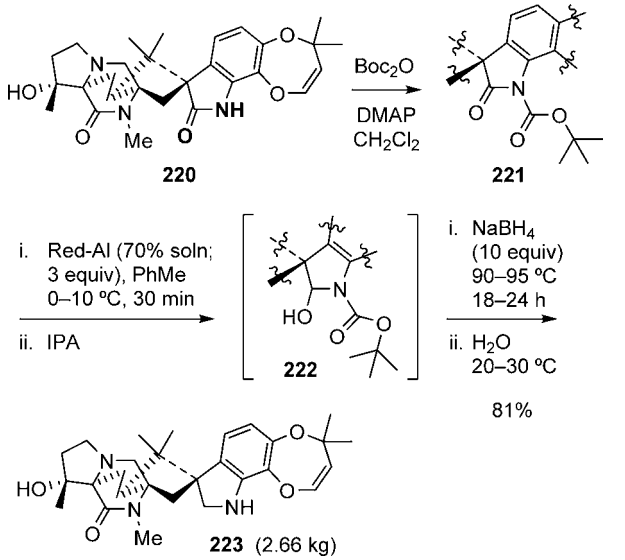


Early two-step conversions of phthalimides to isoindolines converted **215** to isoindole **219** via Red-Al at 85 °C and further reduced the isoindole to isoindoline **216** using $NaBH(OAc)_3$. Several reagents were explored for the direct transformation of phthalimide to isoindoline, and LAH·2THF (prepared in situ from LAH and 2 equiv THF) in toluene at relatively low temperature (0−20 °C) effected this reduction while minimizing the formation of isoindole **219** and defluorination byproducts **217** and **218**. Whereas the double carbonyl reduction of imides to the fully saturated amines typically requires forcing conditions, the aromatic ring of the phthalimide enables ionization (and reduction) of the hemiaminal intermediate at lower temperatures via resonance stabilization of the carbocation. The soluble LAH·2THF complex in toluene offered the additional process benefits of homogeneous solutions and easy removal of aluminum salts on workup (vide infra). This reducing agent was freshly prepared by dosing a slurry of LAH in toluene with 2 equiv of THF, and the homogeneous solution was cooled at 0 °C as phthalimide **215** was added in portions over 1.5 h while maintaining an internal temperature below 8 °C. The resulting solution was held at 20 °C until reaction completion, cooled to 0 °C, and slowly quenched with water while maintaining internal temperature below 15−20 °C to avoid oxidation. THF was also added during the reactive quench to enhance the solubility of **216** and promote better mixing of the aluminum salts. The mixture was passed through a Nutsche filter to remove the aluminum salts, and the filtrate was treated with aqueous washes, dried, and concentrated to 2.4 kg of isoindoline **216** containing 7% isoindole **219** (purged downstream).

7.2. Imide Reduction to Hemiaminal. As discussed in the previous section, imides and similar functionalities (e.g., *N*-acyl carbamates) are reduced to the hemiaminal under nonforcing conditions. Metal borohydrides are typical reagents for this transformation on process scale,[68c,121] whereas Red-Al[119] and DIBAL[122] have also been used to form the hemiaminal.

Mauragis and co-workers at Pharmacia developed the selective reduction of a secondary amide in the presence of a tertiary amide for the synthesis of anthelmintic drug candidate **223** (Scheme 57).[119] Secondary amide **220** was first protected

Scheme 57. Selective reduction of secondary amide 220 via imide-type 221 in the presence of a tertiary amide



as imide-type *N*-Boc **221**, which was cooled in toluene and dosed with Red-Al while maintaining an internal temperature of 0−10 °C. After complete consumption of **221**, the reaction mixture was charged with IPA to cleave the aluminate and liberate hemiaminal **222**. This IPA quench was vital to the success of subsequent urethane reduction. The resulting solution was transferred to another tank containing 10 equiv of neat $NaBH_4$, and the slurry was heated at 90−95 °C for 18−24 h. (Again, an excellent example of forcing conditions required to further reduce hemiaminal intermediates from imide-type reduction.) Acidic aqueous media were avoided for quench due to concerns over hydrolysis of the vinylic ether linkage. Instead, the mixture was quenched at 20−30 °C with water, which precipitated boronates and unreacted sodium borohydride from solution. These precipitates were separated via Celite filtration, and special care was taken to dry and package the $NaBH_4$-containing filter cake as hazardous waste. (Maugaris comments that safety concerns about handling reactive waste would require attention before repeating this workup on substantially larger scale.) Desired **223** was crystallized from the filtrate via $EtOH/H_2O$ to afford 2.66 kg of reduced secondary amide.

Molinaro, Hughes, and co-workers at Merck optimized the regioselective reduction of succinimide **224** en route to EP4 antagonist **228**, a treatment for chronic inflammation (Scheme 58).[122] Similar regioselective reductions of quinolinimides via $NaBH_4/Mg(ClO_4)_2$ proceed via chelation of the pyridine and proximal carbonyl;[123] however, **224** contains an arene spacer between the pyridine and imide which prevents

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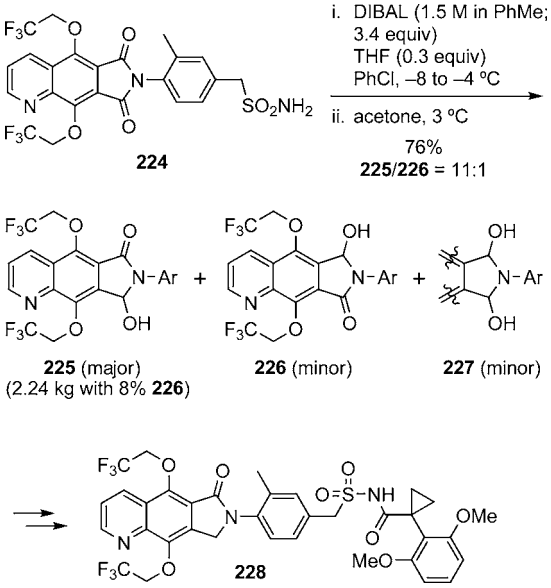
Scheme 58. Regioselective DIBAL reduction of 224 via remote electronic control

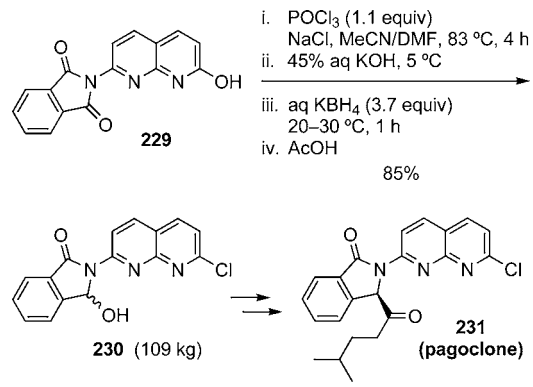


direct chelation, and therefore differences in carbonyl selectivity were attributed to remote electronic control. Several reagents were explored for the regioselective reduction of **224**; all provided mixtures of **225**, **226**, and over-reduced byproduct **227**, and DIBAL afforded the greatest regioselectivity for **225**. A relatively large excess of DIBAL (3.4 equiv) was required to fully consume the imide, presumably due to competitive deprotonation of the sulfonamide and coordination to other Lewis basic sites. Yields were improved marginally by using fewer equivalents of DIBAL in conjunction with an additional Lewis acid (Et_2Zn, Et_3Al), and the best yields were realized in the presence of THF additive (0.3–0.7 equiv) after replacing toluene with chlorobenzene. (The exact role of THF was unknown.) Interestingly, the ratio of **225** to **226** improved with the conversion of imide **224**, suggesting that the minor regioisomer **226** undergoes reduction to the bis(hemiaminal) **227** faster than desired regioisomer **225**. On kilogram scale, these optimized conditions provided an 11:1 ratio of **225** to **226**. Quenching the reaction mixture with acetone minimized the evolution of hydrogen gas during subsequent aqueous workup, which used tartaric acid to purge aluminum salts and minimize emulsions.

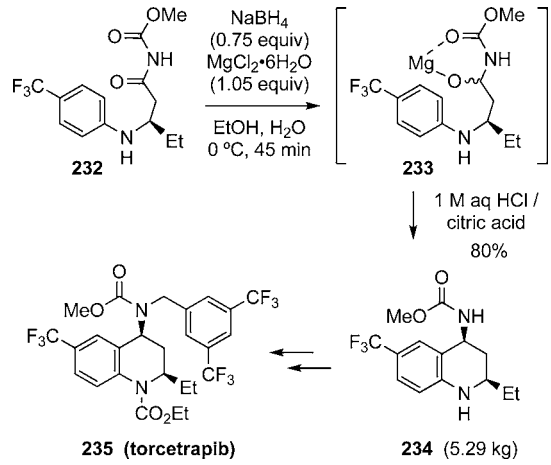
Stuk and co-workers at Pfizer converted succinimide **229** to hemiaminal **230** on very large scale (>100 kg) for the synthesis of pagoclone (**231**), a partial agonist for the $GABA_A$ receptor (Scheme 59).[121b] In a one-pot chlorination/reduction process, the hydroxyl of **229** was first converted to chloride via $POCl_3$. Quenching with aqueous KOH to pH 8 provided an aqueous solution that was dosed with KBH_4 at 0–10 °C and warmed to 20–30 °C. After reduction and AcOH quench, 109 kg of **230** were filtered directly from the mixture for an 85% overall yield.

Scott and co-workers at Pfizer employed a one-pot reduction of imide-type **232** to hemiaminal and stereoselective cyclization for their synthesis of torcetrapib (**235**), a treatment for cardiovascular diseases via the inhibition of cholesteryl ester transfer protein (Scheme 60).[121a] *N*-Acyl carbamate **232** was reduced using a combination of $NaBH_4$ and $MgCl_2$. The magnesium salt served the dual purposes of activating the imide carbonyl for reduction (no reaction was observed with $NaBH_4$

Scheme 59. One-pot chlorination and reduction of 229 to hemiaminal 230



Scheme 60. Reduction/cyclization route to the torcetrapib core



alone) and preventing over-reduction by stabilizing the hemiaminal salt **233** as a Mg-chelate with the adjacent carbonyl. Over-reduction was a prominent side reaction in early runs using $CaCl_2$ in place of $MgCl_2$, as the analogous Ca-chelate proved less stable under reduction conditions. On kilogram scale, a solution of imide **232** in EtOH/H_2O was charged with $NaBH_4$ in the form of 11-mm pellets for increased process safety and ease of handling. No reduction was observed as the suspension was cooled to −10 °C, and then an aqueous solution of $MgCl_2$ (prepared from the hexahydrate) was added at a rate to maintain an internal temperature below −5 °C. The solution was held at 0 °C until reaction completion and then was transferred to a mixture of aqueous 1 M HCl, citric acid, and CH_2Cl_2. This acid quench, which liberated H_2, converted **233** to **234** as a single diastereomer via dehydration to imine (not shown) and cyclization. Complexation of Mg to citric acid purged this metal and minimized emulsions on workup. Additional extractions, carbon treatment, and crystallization from CH_2Cl_2/hexanes provided **234** in 80% overall yield.

8. ACID CHLORIDE REDUCTION TO ALDEHYDE

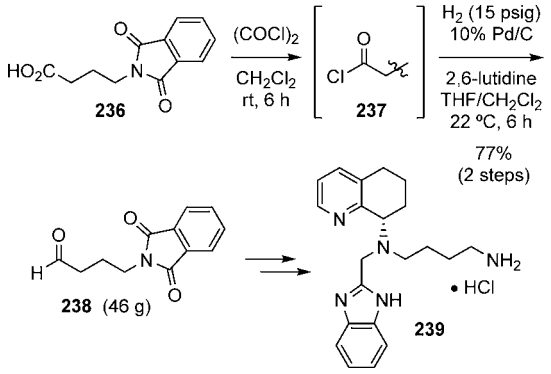
This transformation is rarely found in the large-scale literature, since the usual approach to convert acids to aldehydes is via reduction to the alcohol followed by oxidation. The Rosenmund reduction (catalytic hydrogenation)[124] is the most common procedure and requires the use of a deactivated catalyst (normally Pd·$BaSO_4$) to prevent further reduction of the aldehyde to the

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156–1184

alcohol.[125] Et_3SiH can be used as an alternative to hydrogen gas.[125]

Crawford and co-workers at AnorMED, a subsidiary of Genzyme, have reported the preparation of CXCR4 chemokine receptor antagonist **239**, a candidate for HIV entry inhibition (Scheme 61).[126] Aldehyde intermediate **238** was accessed via

Scheme 61. Rosenmund reduction of acid chloride 237 to aldehyde 238



the Rosenmund reduction of acid chloride **237**, which in turn was prepared by treating acid **236** with oxalyl chloride in CH_2Cl_2. The hydrogenation of **237** with 10% Pd/C and 2,6-lutidine in THF/CH_2Cl_2 was carried out under 15 psig of H_2 and was complete in 6 h. After an aqueous workup, aldehyde **238** was crystallized from heptane/CH_2Cl_2 in 77% yield over the two steps. Key to obtaining clean reduction product was the complete removal of *p*-TsOH employed in the previous preparation of **236** from 4-aminobutytic acid and phthalic anhydride; otherwise, 4-methylbenezenethiol was generated under the reaction conditions (via *p*-TsOH reduction), which led to catalyst poisoning and the formation of thioester **240** (Figure 4). This hydrogenation has been run on 30 kg-scale.

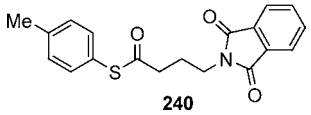


Figure 4. Hydrogenation byproduct **240** generated after *p*-TsOH reduction.

9. CONCLUSIONS

As this review has demonstrated, the reduction of carbonyl groups is common practice today during large-scale operations across the pharmaceutical industry. Today's process chemist can choose from a wide variety of reducing agents, especially in early development where cost considerations are not as important as in late development. Many of these technologies are mature and can be implemented with confidence on a broad range of substrates, even though optimization of reaction conditions (e.g., nature of reductant, solvent, temperature, workup, etc.) may be required to obtain the satisfactory results. Boron-based reductants are overwhelmingly the preferred choice for the reduction of aldehydes, ketones, carboxylic acids, esters, and amides because of their diversity, chemoselectivity, and commercial availability (in many cases as solutions, which facilitates their use in the kilo lab or pilot-plant facilities).

Several trends in large-scale carbonyl reduction can be observed from this review:

1 $NaBH_4$ is the most versatile reductant, either by itself or in combination with other reagents which activate the carbonyl for reduction. Its low cost (per mole of hydride), stability, reliability, and commercial availability in various forms (as a solid or in caustic, aqueous solution) are key factors for its widespread use.
2 Somewhat surprisingly, the reduction of aldehydes to alcohols is rarely performed for the large-scale synthesis of pharmaceuticals. Aldehydes are relatively unstable substrates prone to oxidation and epimerization at the α-carbon (if a stereogenic center is present), and as a consequence, process chemists may try to avoid incorporating them into synthetic routes. At the same time, aldehydes are versatile functional groups, and those which do find their way into process routes are often derivatized in other transformations beyond simple reduction to alcohol. Drug substances do not typically contain the aldehyde functionality, and it may be more practical to design routes that include other functional groups which are less reactive, such as esters, that can also eventually be converted to the alcohol.
3 The reduction of prochiral ketones to the corresponding chiral alcohols, arguably one of the most common transformations, can be successfully implemented with very high selectivity through a number of methods. Catalytic protocols are particularly important, such as oxazaborolidine-mediated reductions, which facilitate workup and purification in contrast to more traditional methods that employ pinene-derived reagents. Many of today's drugs (or drug candidates) contain stereogenic centers, and asymmetric ketone reduction is an excellent strategy for introducing stereocenters into API or earlier intermediates. The chiral alcohol product may be the final target or provide a convenient handle for further derivatization.
4 Acids are common substrates for reductions, and a large number of reagents will effect this transformation. A convenient feature is that acids can be chemoselectively reduced to alcohols in the presence of an ester.
5 Ester reduction is very common and encompasses one of the largest sections in this review. Contributing factors are the relative stability of this functional group and the possibility for easy derivatization, which turns esters into masked alcohols, acids, or even aldehydes. Most examples are for conversion to the corresponding alcohol, since it is difficult to reliably stop the reduction at the aldehyde stage. An exception to the latter is the conversion of lactones to lactols, exemplified by several cases in this review.
6 Amides are most commonly reduced to the saturated amine (and not to the alcohol as per ester reductions). Imides may also be reduced at both carbonyls to the saturated amine, although forcing conditions may be required to convert hemiaminal intermediates.

Finally, environmental considerations are high priority when the costs of waste disposal can negatively impact the scalability

dx.doi.org/10.1021/op2003826 | Org. Process Res. Dev. 2012, 16, 1156–1184

and appeal of a reduction process. The continued development of greener technologies should further the advancement of carbonyl reductions throughout industry.[127]

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Jaan Pesti for very helpful discussions on the format and scope of this review during our planning and composition of this manuscript. We also thank the reviewers for alerting us to references 18 and 75.

ABBREVIATIONS

BDPP: 2,4-bis(diphenylphosphino)pentane
CDMT: 2-chloro-4,6-dimethoxy-1,3,5-triazine
COD: 1,5-cyclooctadiene
dadmp: 4-dimethylamino-3,5-dimethylphenyl
DAIPEN: 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine
DMTMM: 4-(4,6-dimethoxy-1,3,5-triazine-2-yl)-4-methylmorpholinium chloride
dpen: 1,2-diphenylethylenediamine
eda: ethylenediamine
Pica: α-picolylamine
PMHS: poly(methylhydrosiloxane)
TsCYDN: (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine
TsDPEN: (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenyl-1,2-ethanediamine
Xyl-P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethlyphenyl)phosphino]-3,3′-bilyridinyl
XylSkewphos: 2,4-bis(di-3,5-xylylphosphino)pentane

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