Unlocking the Potential of Asymmetric Hydrogenation at Merck

C. SCOTT SHULTZ* AND SHANE W. KRSKA*

Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065-0900

Received June 11, 2007

ABSTRACT

This Account outlines the efforts of Merck scientists toward implementing asymmetric hydrogenation as a core competency within Merck Research Laboratories. Several key factors are discussed including (i) a focus on efficient chemical synthesis, (ii) implementation of high throughput screening (HTS) techniques, (iii) demonstration of robustness on scale, and (iv) diligence to ensure freedom of operation and catalyst supply for manufacturing. Several examples of the development of efficient asymmetric hydrogenation processes are described.

Introduction

Industrial chemical synthesis of pharmaceuticals presents a number of unique challenges and opportunities as the relatively high chemical complexity of most small molecule pharmaceutical drugs requires multistep syntheses incorporating a wide variety of organic transformations. Fortunately, the high value of these compounds greatly increases the scope of chemistry methodologies that could be considered economically viable, especially when compared with what could be considered for higher volume, lower cost products such as agrochemicals. In this context, the pharmaceutical industry was an early adopter of many catalytic methodologies, both as an enabler of drug discovery and as efficient means to convergent syntheses of highly functionalized molecules on the pilot plant and factory scale. The Merck Process Research department has a long history in this regard, from early studies in chiral phase-transfer catalysis[1] to work with Pd-catalyzed cross-coupling chemistry,[2] and even design of chiral ligands for asymmetric hydrogenation.[3]

In recent years, the increasingly competitive environment in the pharmaceutical industry, as exemplified by ever-shortening periods of marketing exclusivity for first-in-class drugs,[4] has placed enormous pressure on companies to bring products to market faster. For the process chemist, this means less time to explore and develop robust, scaleable synthetic routes and hence the need to rapidly assess the viability of key synthetic steps, especially those that set product stereochemistry. Add to this the increasing number of chiral drug candidates in development,[5] and one can readily see the need for the pharmaceutical industry to embrace catalytic methodologies like asymmetric hydrogenation that offer the promise of rapid, efficient access to chiral molecules with a high probability of success.

It is surprising then that Merck, not unlike like the rest of the pharmaceutical and fine chemicals industries, was slow to adopt asymmetric hydrogenation as a methodology of choice for synthesizing chiral molecules with only ca. 10 instances of asymmetric hydrogenation implemented industry-wide as of 2001.[6] Beyond a few isolated examples,[7] Merck's interest in asymmetric hydrogenation remained sporadic until 2002. A number of factors contributed to this situation, including uncertainty around cost and freedom of operation involving negotiations with catalyst vendors, perceived difficulties with air sensitivity and reaction robustness upon scale-up, need for specialized equipment and expertise in screening, and efficient access to the large number of commercially available chiral ligands and catalysts.

The Merck Catalysis Laboratory was formed in 2002 as a joint effort between the Chemical Engineering and Process Research departments to address these barriers to the utilization of asymmetric hydrogenation at Merck. Originally consisting of a group of seven dedicated organic and organometallic chemists, the Laboratory's mission was to facilitate incorporation of asymmetric hydrogenation into Merck drug candidate syntheses at all stages of development, from those that support preclinical animal safety studies all the way through commercialization. With a focus on overall synthetic efficiency, the Laboratory always strove to "make the catalytic step fit the process" rather than forcing the project team to divert the synthetic route to intermediates that were well-precedented to work in the asymmetric hydrogenation step. This philosophy led us to explore asymmetric hydrogenations of substrate classes with little or no precedence in the literature—several examples of this type are given below. To accomplish this, the Catalysis Laboratory needed to develop robust, efficient means to screen the large number of available chiral catalysts as fast as possible using the least amount of valuable intermediate. The evolution of our screening techniques is also presented below.

A Focus on Efficient Chemical Syntheses

While the sensible use of protecting groups can provide quick access to desired reactivity, the unsavory atom economy and cost of additional processing steps dictates that project teams seek out direct methods to the desired

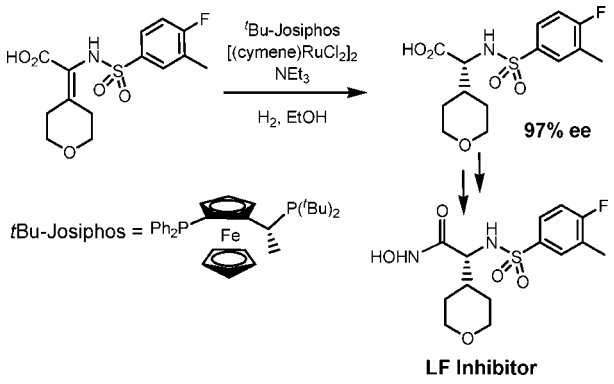
Scott Shultz was born in Scottsville, AL, in 1974. After he received his B.A. in chemistry from Transylvania University (Lexington, KY) in 1996, he completed his Ph.D. in organometallic chemistry at the University of North Carolina at Chapel Hill in 2001 under the direction of Maurice Brookhart. He started at Merck in the Reaction Engineering Laboratory in 2001 and is currently a Research Fellow in the Merck Catalysis Laboratory with responsibility for the high throughput screening workflow.

Shane Krska was born in Deadwood, SD (1970). He received his B.S. (1992) from the South Dakota School of Mines and Technology in Rapid City, SD, and his Ph.D. (1997) from MIT, working with Professor Dietmar Seyferth. After postdoctoral training in the laboratories of Professor Robert G. Bergman at U.C. Berkeley, he joined Merck Research Laboratories in 1999. He is currently a Senior Investigator in the Merck Catalysis Laboratory.

* E-mail addresses: scott_shultz@merck.com; shane_krska@merck.com.

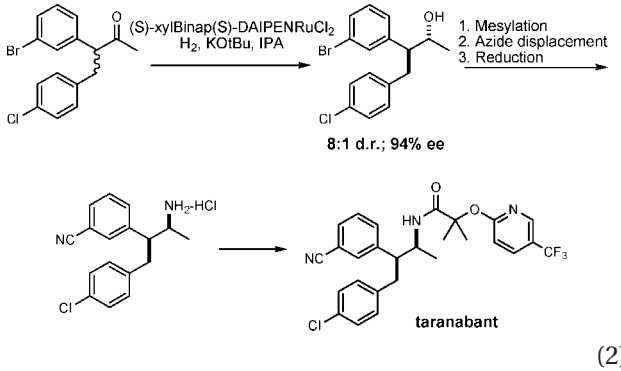
10.1021/ar700141v CCC: $37.00
Published on Web 11/20/2007

chemical intermediates. For the synthesis of chiral amino acid derivatives, the use of amide or carbamate protecting groups has been widely practiced, and for the synthesis of Merck's Anthrax Lethal Factor inhibitor (eq 1), we could have hydrogenated the acetamide-methyl ester of the tetrahydropyran intermediate, which has been demonstrated by Burk in 98% ee with (Me-BPE)Rh(COD)OTf.[8] To avoid the extra steps of exchanging the acetyl group for the desired sulfonyl side chain, though, we attempted an unprecedented direct hydrogenation of the N-sulfonylated intermediate. The presence of the very electron-deficient sulfonamide group does reduce the reactivity of our substrate toward rhodium catalysts; however, high-throughput screening (HTS) allowed us to rapidly screen other metals and conditions and the highly selective *t*Bu-Josiphos/$[(cymene)RuCl_2]_2$ catalyst system was rapidly identified. The desired chiral sulfonamide was therefore accessed in 97% ee and 98% yield.[9]



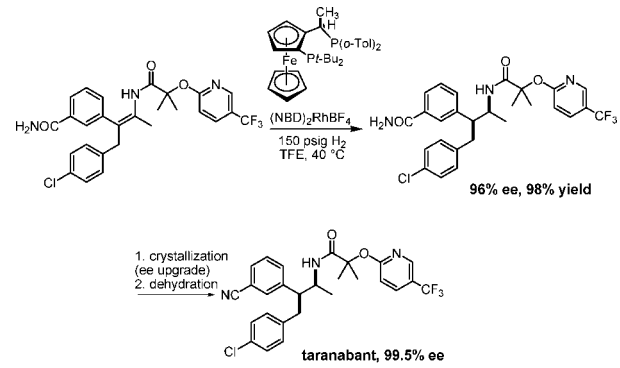
(1)

The use of the appropriate "protecting group" or substituent was again demonstrated in the synthesis of taranabant, a CB-1R inverse agonist for the treatment of obesity. The two contiguous stereocenters in taranabant can be accessed via several strategies, and early on dynamic kinetic resolution (DKR) of the racemic bromoketone (eq 2) was employed.[10] This strategy provided access to the key chiral alcohol in excellent enantioselectivity and good diastereoselectivity. DKR-hydrogenation is an efficient and elegant reaction; however, three more steps including the use of sodium azide were necessary to access the desired chiral amine.



(2)

Setting both stereocenters in a single transformation remained a motivating factor for the project team, and therefore the direct hydrogenation of a tetrasubstituted enamide was investigated (eq 3).[11] While a simple amide or carbamate protecting group could have been employed, the enamide was constructed with the full side chain so that the basic connectivity in taranabant could be accessed directly. Since there were only a few accounts demonstrating successful hydrogenation of similarly sterically congested enamides,[12] we were pleased to discover the catalyst consisting of a cationic rhodium precursor with a modified Josiphos ligand provided the benzamide-chiral amide under very mild conditions with only 0.15 mol % catalyst (eq 3). Key to this hydrogenation was the use of 2,2,2-trifluoroethanol (TFE), which allowed us to lower the catalyst loading by more than a factor of 10. While we were unable to efficiently carry the benzonitrile moiety through the hydrogenation sequence due to catalyst inhibition and competitive reduction, crystallization of the benzamide-chiral amide fortuitously provided pure material with an ee of 99.5%.



(3)

The selection of the optimal place to incorporate an asymmetric hydrogenation step in a drug synthesis can have significant impact on the overall manufacturing cost. Traditionally the chiral fragment(s) may be incorporated in an early step of a synthesis if a simple chiral building block is readily available or if known chemistry can be used directly with little development. However, an asymmetric hydrogenation is often the most expensive step to run due to the typically high cost of a chiral catalyst or reagent. Thus, incorporation of an expensive asymmetric hydrogenation step early in the synthesis will negatively impact the overall cost if there are low yielding steps downstream or if multiple transformations must be accomplished in series. For example, in a five-step sequence with an average step yield of 85%, running the asymmetric hydrogenation as the first step in the synthesis means processing approximately twice as many moles of intermediate in that step vs the scenario where the asymmetric hydrogenation is the final chemical transformation in the sequence. The magnitude of the impact on the process economics depends on a variety of factors; however, for the above example, using 0.5 mol % of a catalyst with FW = 500 g/mol at a cost of $100/g would translate to $0.5 M of increased raw material cost per metric ton of drug

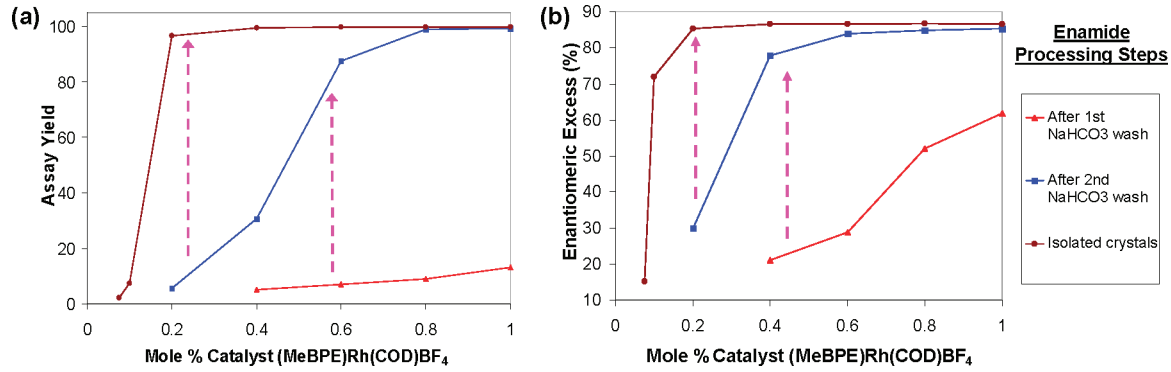
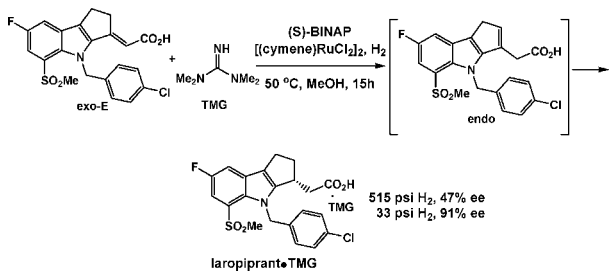


FIGURE 1. Evaluation of (a) assay yield and (b) enantiomeric excess as a function of catalyst loading and purification step.

produced (drug FW = 500 g/mol). On the other hand, incorporating the asymmetric hydrogenation late in the synthesis offers fewer opportunities for chiral purity upgrade and heavy metal impurity removal, but these difficulties are generally overcome in the course of development.

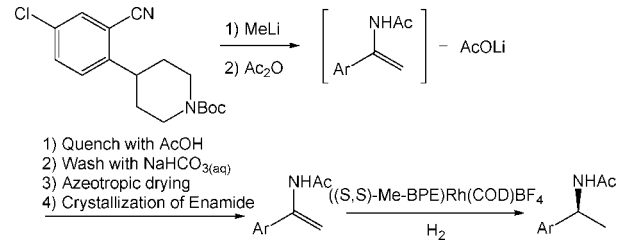
Another example of a late stage asymmetric hydrogenation that also demonstrates novel reactivity is the case of laropiprant, a prostaglandin D_2 (PGD_2) receptor antagonist.[13] This is the only published example of asymmetric hydrogenation of an exocyclic α,β-unsaturated carboxylic acid. Interestingly, careful mechanistic investigations revealed that this hydrogenation proceeds largely through the endo isomer at low hydrogen pressure. This information was crucial for the successful scale-up and implementation of this process because the endo isomer gives higher enantioselectivity with BINAP/[(cymene)$RuCl_2]_2$ catalyst than direct hydrogenation of the exo-E isomer at higher pressure.



(4)

Ensuring Catalyst Performance on Scale

Achieving high catalyst efficiencies (TON) while maintaining performance (ee, de, etc.) is often critical for economic as well as processing reasons (metal removal, for example), and exhaustive purification of raw materials can often be required (chromatography, distillation, resin treatments, crystallization, etc.) Such was the case in the asymmetric hydrogenation of the Boc-piperidine-substituted enamide (eq 5).[14] During the first bulk scale up, catalyst performance (yield and ee) was observed to vary from lot to lot of enamide. A more careful examination of the workup procedure for the enamide substrate quickly revealed that process impurities were responsible for the variability in the hydrogenation. In a single experiment, we varied the substrate to catalyst ratio for material pulled after each step in the purification and isolation of the enamide (Figure 1). From the data, it is clear that the efficiency of the first $NaHCO_3$(aq) wash was not sufficient to remove all catalyst poisons. By taking advantage of parallel experimentation, the project team was able to develop and implement a robust process in a matter of a few days.



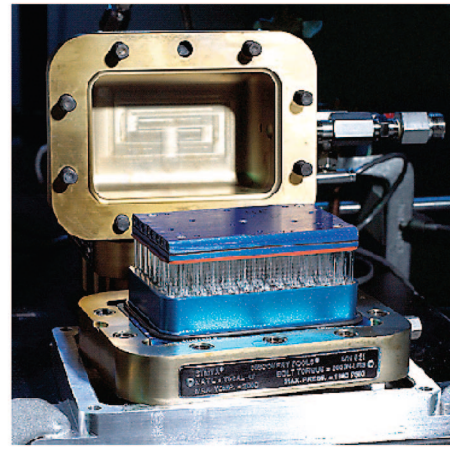
(5)

High-Throughput Screening Is an Enabling Paradigm

HTS for the identification of highly enantioselective and efficient catalyst systems for pharmaceutical synthesis is absolutely imperative with the tough challenges facing process development in recent years (e.g., reduction in development cycle times and limited research funding). While there are a few chiral ligands that have shown some generality in asymmetric transformations (e.g., DuPhos and BINAP), the diversity in chemical structures in pharmaceutical process chemistry necessitates that a truly diverse set of chiral catalysts be evaluated to discover and develop highly efficient asymmetric chemical processes. There are at least 16 chiral catalyst systems that are reported to give ≥95% ee for methyl acetamidocinnamate (MAC);[15] however, the asymmetric hydrogenation substrates we have encountered can be far more complex.[16] Additionally, it is often the case that there is little or no literature precedent for asymmetric hydrogenation of a given substrate, and therefore it is imperative to screen a wide range of catalysts covering a large amount of chiral "space" to find a suitable catalyst system.

Prior to 2004, we made heavy use of simple yet versatile glass pressure vessels for reaction screening (Figure 3). Individual reactions (typically 0.5–1 mL) were carried out in 8 mL glass vials fitted with septum caps and vent needles. This allowed us to simultaneously screen six

Glass Pressure Vessels



Symyx High Pressure Blocks

FIGURE 2. Hydrogenation screening equipment.

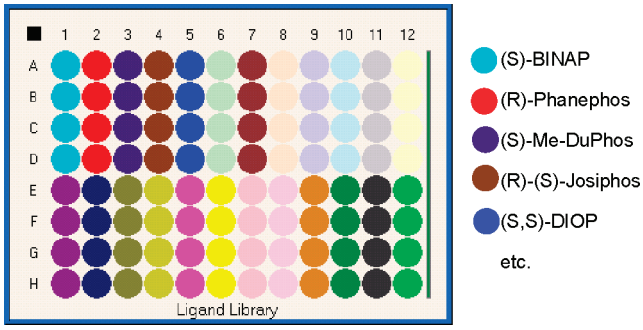


FIGURE 3. Example of a typical ligand library consisting of 4 copies of 24 unique chiral ligands.

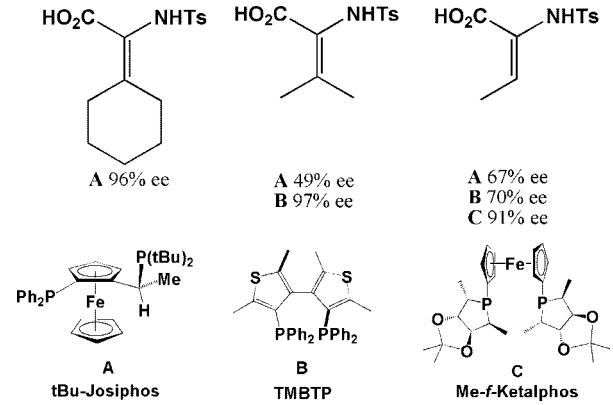


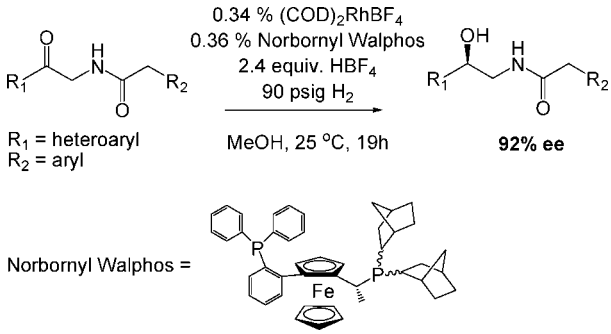
FIGURE 4. Hydrogenation of *N*-Ts-α-dehydroamino acids.

different conditions at a single temperature and pressure. Each reaction was individually prepared, and the pressure vessel was assembled in a nitrogen-filled glovebox. This was a highly reliable setup for reaction screening, albeit with low overall throughput. From here, the acquisition of Symyx HTS equipment such as the high-pressure reaction blocks (Figure 2) that can be used in conjunction with automated liquid handling equipment led to substantial gains in throughput.[17] For the first time at Merck, it was now possible to screen the hundreds of permutations (ligand/metal precursor/solvent/additives, etc.) necessary to develop robust, efficient asymmetric hydrogenation reactions in a truly efficient and rapid manner. In addition to providing increased throughput, the parallel reaction blocks also utilize a lower reaction volume (typically 0.1–0.3 mL), thereby requiring much less hydrogenation substrate per reaction. This has even greater implications as we are now able to impact drug synthesis earlier in the development cycle.

In order to accelerate the time to discover a hit, we moved from a rather unsystematic method of choosing individual catalysts for evaluation to a library-based approach. By predispensing chiral ligands into 96-well microtiter plates and using automated or semiautomated liquid handling equipment, it was possible to screen hundreds of ligands under multiple conditions in a single day.[18] For example, as is graphically illustrated in Figure 3, a library of chiral ligands could consist of 4 copies of 24 unique ligands arrayed in an 8 × 12 format. Addition of stock solutions of catalyst precursors such as $[(\text{cymene})\text{RuCl}]_2$ or $(\text{COD})_2\text{RhBF}_4$, substrate, and optional additives is then accomplished in short order, and the screening of tens to hundreds of catalysts under a variety of conditions becomes straightforward.

The impact of HTS is nicely illustrated with the following examples from our laboratories. Since small changes to even relatively simple molecules can necessitate the use of very different ligands to achieve high enantioselectivity, HTS played a major role in our investigations into the ruthenium-catalyzed asymmetric hydrogenation (AH) of various *N*-Ts-α-dehydroamino acids (Figure 4).[9] While the ^{t}Bu-Josiphos ligand **A** gave acceptable results with the cyclohexyl substrate, enantioselectivity was quite poor for the valine derivative with this ligand. In a second round of screening, we observed the TMBTP ligand (**B**) to give excellent ee for the valine substrate. A third round of screening was necessary for the 2-Me substrate because ligands **A** and **B** provided inadequate enantioselectivity. Ultimately good ee was obtained with the Me-*f*-Ketalphos ligand. Prior to the implementation of HTS, such extensive catalyst screening would have required weeks or months of experimentation but in this case was accomplished in a matter of days.

Another example that illustrates the need for an unbiased and diverse ligand screen is that of the ketoamide hydrogenation shown in eq 6. In our internal development work, out of several ligand libraries that were screened (>100 ligands), the Rh catalyst containing the bis-2-norbornyl-substituted Walphos ligand was observed to give excellent enantioselectivity and reactivity.[19] This ligand is synthesized from di-2-norbornylphosphine, which is a mixture of endo and exo isomers. It is not plausible to think that one could predict *a priori* that this ligand (a mixture of four diastereomers!)[20] would provide this level of asymmetric induction.



(6)

Freedom of Operation and Catalyst Supply

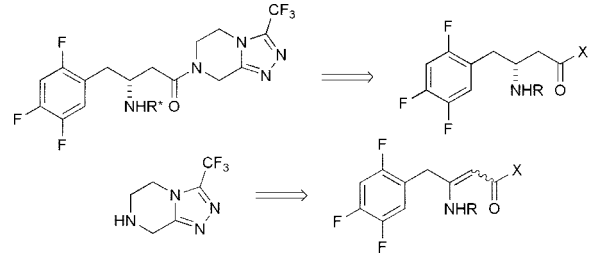
There were a number of business considerations that had to be addressed early so that asymmetric hydrogenation technology could be introduced more broadly into Merck drug syntheses. The overall value of a chiral ligand or catalyst is only partly determined by chemistry. Small differences in performance (ee, yield) will often be outweighed by cost and availability. The cost of a chiral ligand arises from several issues including complexity, availability, and intellectual property (IP) rights.[21] Introducing an asymmetric step early in the development cycle for a drug candidate means that there is ample time to address not just chemical processing issues but also the supply and cost issues, both of which must be addressed prior to bulk drug manufacturing, thereby reducing the risk of incorporating a patented technology into a manufacturing synthesis.

The Development of the Sitagliptin Asymmetric Hydrogenation

The story of the development of an unprecedented asymmetric hydrogenation of an unprotected enamine as part of the manufacturing process for sitagliptin illustrates well all the key success factors that have been emphasized so far in this Account. In addition, as one of the first projects handed to the newly formed Catalysis Laboratory in the fall of 2002, the success of this endeavor paved the way for many of the projects that followed later.

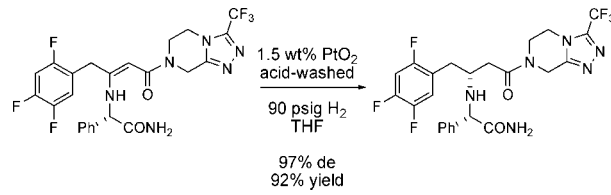
In October 2006, sitagliptin was approved by the U.S. FDA as the first and only entry in the new breakthrough class of orally active agents, known as DPP-4 inhibitors, for the treatment of type 2 diabetes and is now being marketed by Merck as a monotherapy under the brand

Scheme 1. Retrosynthesis of Sitagliptin



name Januvia and as a combination with metformin under the brand name Janumet. In the summer of 2002, the sitagliptin project was progressing at a rapid pace through the Merck drug development process. An interim route had been developed that was capable of reliably yielding sitagliptin on a multikilogram scale for support of ongoing clinical trials.[22] Although the overall yield of the route (52%) was high, the length of the synthesis (nine steps), the use of relatively expensive reagents (two EDC couplings), and the undesirable waste generated from a Mitsunobu reaction made the chemistry less attractive from a manufacturing perspective. Thus, Process Research undertook an extensive effort to identify a shorter, more cost-effective, and environmentally benign synthesis of sitagliptin. Prior work had established an efficient three-step route to the triazole portion of the molecule,[23] so efforts focused on accessing the β-amino acid functionality. Two approaches were evaluated, a substrate-controlled diastereoselective heterogeneous hydrogenation of an enamine/enamide bearing a chiral auxiliary and a catalyst-controlled asymmetric hydrogenation of an enamine/enamide (Scheme 1).

For the substrate-control approach, the team identified (*S*)-phenylglycine amide (PGA) as a suitable chiral auxiliary that gave remarkably high diastereoselectivity in the hydrogenation using Adam's catalyst (eq 7).[24] Treatment of the triazole-bearing β-ketoamide with (*S*)-PGA gave exclusively the (*Z*)-PGA-enamine in excellent yield and purity. Subsequent diastereoselective hydrogenation, followed by hydrogenolytic removal of the chiral auxiliary using Pearlman's catalyst gave the free base of sitagliptin in excellent yield and purity. Key to the success of the diastereoselective hydrogenation was acid washing of the Adam's catalyst, resulting in both high diastereoselectivity and activity. This method was found to be quite general for the synthesis of a variety of 3-alkyl and -aryl-substituted β-amino acid derivatives and has given the highest reported levels of diastereoselectivity (up to 99%) for such a system.

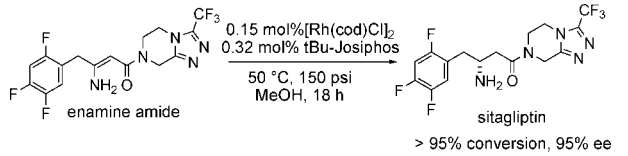


(7)

For the catalyst-control approach, ample literature precedent suggested that asymmetric hydrogenation of a

dehydro-β-amino acid derivative with a suitable N-protecting group would be successful, provided a way could be found to synthesize the unsaturated substrate with acceptable control of olefin geometry.[25] However the project team had been tasked with finding an efficient synthesis of sitagliptin, and the protection/deprotection sequence required in such an approach would add unnecessary steps to the overall route. Thus, the team decided to explore the asymmetric hydrogenation of the *unprotected* enamine, despite literature reports suggesting that substrates of this type were unreactive with typical asymmetric hydrogenation catalysts.[26] The requisite enamine amide (Scheme 1, R = H, X = triazole side chain) was easily obtained by treatment of the corresponding β-ketoamide with NH_4OAc in methanol. Initial catalyst screening with a variety of Rh, Ru, and Ir complexes of traditional chiral bis(phosphine) ligands (e.g., BINAP) indeed showed low reactivity, low enantioselectivity, or both. However, the use of $[(COD)RhCl]_2$ in combination with newer ferrocene-based phosphine ligands such as *t*Bu-Josiphos (Figure 3) gave promising reactivity and enantioselectivity (ee $\geq$ 90%).

At this point, the Catalysis Laboratory joined the effort to turn this promising lead into a practical, scalable process. Since at this point in time Merck had limited experience with scaling asymmetric hydrogenations and had no specific experience working with the Josiphos class of ligands, a strategic partnership was forged with Solvias, AG, the catalyst supplier for Josiphos, which had world-renowned expertise in the field of asymmetric hydrogenation. In a joint effort, Merck and Solvias conducted hundreds of reactions over a very compressed period of three months in order to push the asymmetric hydrogenation reaction to the limits of its performance. Dozens of ligands and additives were screened, along with the usual parameters of solvent, temperature, and pressure. The resulting optimized reaction depicted in eq 8, along with the associated chemistry for synthesizing the enamine amide[27] and the downstream process for enantiopurity upgrade and final salt formation, was subsequently run in the pilot plant on a hundreds of kilograms scale, less than 6 months after its discovery. Indeed, in the year following the development of the asymmetric hydrogenation route, over 1 MT of sitagliptin was produced in this manner, and over 20 MT has been produced to date.



(8)

Concluding Remarks and Outlook

In this Account, we have clearly demonstrated with numerous examples how we have implemented an HTS approach to developing asymmetric hydrogenation reactions for pharmaceutical drug synthesis at Merck. When one considers both the breadth of chemical diversity encountered in small molecule drug synthesis and the difficulties often encountered with ensuring freedom of operation for manufacturing, then the flexibility and efficiency that HTS offers becomes apparent. With the speed that HTS has brought to the Merck Catalysis Laboratory, we have had the opportunity to impact a broad range of the drug development cycle from preclinical drug supply (grams) to bulk manufacturing (metric tons). By taking advantage of technological advances in automation workflows, we have taken novel and powerful chemistry from the academic realm and implemented it as a platform technology for Merck Process Research. Finally, we believe firmly that the model we have implemented for asymmetric hydrogenation at Merck should apply to other emerging chemistries as well.

We would like to thank our Merck colleagues in Process Research, Early Development Analytical Research, and Global Pharmaceutical Commercialization with whom we have worked closely over the years. The research and methodology presented in this Account was carried out under the leadership of Dr. Yongkui Sun, and we thank the following individuals for contributions: Dr. Chris McWilliams, Dr. Thorsten Rosner, Dr. David Tellers, Dr. Yi Xiao, Chaoxian Cai, Peter Huefner, Jess Sager, and Dr. Rick Sidler. Additionally, we extend special appreciation to the following colleagues for research, technical, legal, and procurement support: Phil Durette, Mel Winokur, Andrew Shigo, Tyrell Rivers, Julie Pentz, John Finn, Dr. Chris Welch, Mirlinda Biba, Peter Sajonz, Anthony Houck, Charles Bazaral, and Andrew Newell. Finally, we thank Drs. David Mathre, Richard Tillyer, Ralph P. "Skip" Volante, and Michael P. Thien for their leadership and continued support of the initiative to introduce a focused catalytic screening and optimization effort into Process R&D at Merck.

References

(1) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-Indacrinone via chiral phase-transfer catalysis. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

(2) Yasuda, N. Application of cross-coupling reactions in Merck. *J. Organomet. Chem.* **2002**, *653*, 279–287.

(3) (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. A new planar chiral bisphosphine ligand for asymmetric catalysis: Highly enantioselective yydrogenations under mild conditions. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. [2.2]PHANEPHOS-ruthenium(II) complexes: Highly active asymmetric catalysts for the hydrogenation of beta-ketoesters. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.

(4) DiMasi, J. A.; Paquette, C. The economics of follow-on drug research and development: Trends in entry rates and the timing of development. *Pharmacoeconomics* **2004**, *22* (S2), 1–14.

(5) Rouhi, A. M. Chiral Chemistry: Traditional methods thrive despite numerous hurdles, including tough luck, slow commercialization of catalytic processes. *Chem. Eng. News* **2004**, *82*, 47–62.

(6) Blaser, H.-U.; Spindler, F.; Studer, M. Enantioselective catalysis in fine chemicals production. *Appl. Catal. A: Gen.* **2001**, *221*, 119–143.

(7) (a) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. An efficient asymmetric hydrogenation approach to the synthesis of the Crixivan® piperazine intermediate. *Tetrahedron Lett.* **1998**, *39*, 6823–6826. (b) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. Asymmetric hydrogenation of tetrahydropyrazines: Synthesis of (S)-piperazine-2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.* **1995**, *36*, 6419–6422. (c) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E.J.J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsonola, R. Scalable, efficient process for the synthesis of (R)-3,5-bistrifluo-

romethylphenyl ethanol via catalytic asymmetric transfer hydrogenation and isolation as a DABCO inclusion complex. *Tetrahedron: Asymmetry* **2003**, *14*, 3581–3587. (d) Chung, J. Y. L.; Zhao, D.; Hughes, D. L.; McNamara, J. M.; Grabowski, E. J. J.; Reider, P. J. Asymmetric hydrogenation of 3-alkylidene-2-piperidones using Noyori's catalyst. Effect of N-substituents on the enantioselectivity. *Tetrahedron Lett.* **1995**, *36*, 7379–7382. (e) Hoerrner, R. S.; Askin, D.; Volante, R. P.; Reider, P. J. A highly enantioselective asymmetric hydrogenation route to β-(2R,3S)-methyltryptophan. *Tetrahedron Lett.* **1998**, *39*, 3455–3458.

(8) Burk, M. J.; Gross, M. F.; Martinez, J. P. Asymmetric catalytic synthesis of β-branched, amino acids via highly enantioselective hydrogenation reactions. *J. Am. Chem. Soc.* **1995**, *117*, 9375–9376.

(9) Shultz, C. S.; Dreher, S. D.; Ikemoto, N.; Williams, J. M.; Grabowski, E. J. J.; Krska, S. W.; Sun, Y.; Dormer, P. G.; DiMichele, L. Asymmetric hydrogenation of N-sulfonylated-α-dehydroamino acids: Toward the synthesis of an anthrax lethal factor inhibitor. *Org. Lett.* **2005**, *7*, 3405–3408.

(10) Chen, C.-Y.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack, J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczykowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. W. Catalytic, enantioselective synthesis of taranabant, a novel, acyclic Cannabinoid-1 receptor inverse agonist for the treatment of obesity. *Org. Process Res. Dev.* **2007**, *11*, 616–623.

(11) Campos, K. R.; Wallace, D. J.; Shultz, C. S.; Klapars, A.; Zewge, D.; McWilliams, J. C.; Crump, B.; Phenix, B.; Krska, S. W.; Sun, Y.; Chen, C.-Y.; Spindler, F.; Stereoselective synthesis and asymmetric hydrogenation of tetrasubstituted enamides: Application to the synthesis of a selective Cannabinoid-1 receptor inverse agonist for the treatment of obesity. Manuscript in preparation.

(12) (a) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. Asymmetric hydrogenation ofenamides with Rh-BisP* and Rh-MiniPHOS catalysts. Scope, limitations, and mechanism. *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276. (b) Dupau, P.; Bruneau, C.; Dixneuf, P. H. Enantioselective hydrogenation of the tetrasubstituted C=C bond of enamides catalyzed by a ruthenium catalyst generated in situ. *Adv. Synth. Catal.* **2001**, 331–334. (c) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. Highly enantioselective hydrogenation of cyclic enamides catalyzed by a Rh-PennPhos catalyst. *J. Org. Chem.* **1999**, *64*, 1774–1775.

(13) Tellers, D. M.; McWilliams, J. C.; Humphrey, G.; Journet, M.; DiMichele, L.; Hinksmon, J.; McKeown, A. E.; Rosner, T.; Sun, Y.; Tillyer, R. D. On the mechanism of an asymmetric α,β-unsaturated carboxylic acid hydrogenation: Application to the synthesis of a PGD_2 receptor antagonist. *J. Am. Chem. Soc.* **2006**, *128*, 17063–17073.

(14) Boice, G. N.; McWilliams, J. C.; Murry, J. A.; Savarin, C. G., Stereoselective preparation of 4-aryl piperidine amides by asymmetric hydrogenation of a prochiral enamide and intermediates of this process. World PatentWO2006057904 A1.

(15) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. Selective hydrogenation for fine chemicals: Recent trends and new developments. *Adv. Synth. Catal.* **2003**, *345*, 103–151.

(16) For additional published examples from our labs, see: (a) Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. Enantioselective hydrogenation of an α-alkoxy substituted ketone with chiral ruthenium (phosphinoferrocenyl)oxazoline complexes. *Tetrahedron: Asymmetry* **2006**, *17*, 550–553. (b) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. Enantioselective hydrogenation of α-aryloxy α,β-unsaturated acids. Asymmetric synthesis of α-aryloxycarboxylic acids. *Org. Lett.* **2004**, *6*, 3147–3150. (c) Kosjek, B.; Tellers, D. M.; Biba, M.; Farr, R.; Moore, J. C. Biocatalytic and chemocatalytic approaches to the highly stereoselective 1,2-reduction of an α,β-unsaturated ketone. *Tetrahedron: Asymmetry* **2006**, *17*, 2798–2803.

(17) For additional details on HTS workflow, see: McWilliams, C.; Sidler, D. R.; Sun, Y.; Mathre, D. J. Applying statistical design of experiments and automation to the rapid optimization of metal-catalyzed processes in process development. *J. Assoc. Lab. Automation* **2005**, *10*, 394–407.

(18) For an excellent review of parallel experimentation in the pharmaceutical industry, see: Rubin, E. A.; Tummala, S.; Both, D. A.; Wang, C.; Delaney, E. J. Emerging technologies supporting chemical process R&D and their increasing impact on productivity in the pharmaceutical industry. *Chem. Rev.* **2006**, *106*, 2794–2810.

(19) Shultz, C. S.,Unpublished.

(20) In addition to the endo/endo and exo/exo diastereomers, the ligand stereoisomer containing one endo and one exo norbornane substituent is chiral at phosphorous consequently giving rise to an additional pair of diastereomers.

(21) For an in-depth discussion of intellectual property issues relating to the use of catalytic technology for pharmaceutical manufacturing, see: Hawkins, J. M.; Watson, T. J. N. Asymmetric catalysis in the pharmaceutical industry. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224–3228.

(22) Hansen, K. B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivera, N.; Steinhuebel, D.; Armstrong III, J. D.; Askin, D.; Grabowski, E.J.J. First generation process for the preparation of the DPP-IV inhibitor sitagliptin. *Org. Process Res. Dev.* **2005**, *9*, 634–639.

(23) Balsells, J.; DiMichele, L; Liu, J.; Kubryk, M.; Hansen, K.; Armstrong, J. D., III. Synthesis of [1,2,4]triazolo[4,3-r]piperazines via highly reactive chloromethyloxadiazoles. *Org. Lett.* **2005**, *7*, 1039–1042.

(24) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong, J. D., III; Sun, Y.; Mathre, D. J.; Grabowski, E.J.J.; Tillyer, R. D. Highly diastereoselective heterogeneously catalyzed hydrogenation of enamines for the synthesis of chiral β-amino acid derivatives. *J. Am. Chem. Soc.* **2004**, *126*, 3048–3049.

(25) For a recent review, see: Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. Chiral β-amino acid derivatives via asymmetric hydrogenation. *Org. Process Res. Dev.* **2003**, *7*, 355–361.

(26) Okhuma, T.; Kitamura, M.; Noyori, R., In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima.; I. Ed. VCH; New York; 2000; p 17.

(27) Clausen, A. M.; Dziadul, B.; Cappuccio, K. L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T. M. Identification of ammonium chloride as an effective promoter of the asymmetric hydrogenation of a β-enamine amide. *Org. Process Res. Dev.* **2006**, *10*, 723–726.

AR700141V