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Accelerated Process Development of Pharmaceuticals: Selective Catalytic Hydrogenations of Nitro Compounds Containing Other Functionalities

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Abstract:
The hydrogenation of three different pharmaceutical nitro-containing compounds has been studied using high-throughput experimentation (HTE) methods. Significant improvements to the existing reactions were obtained for two of the examples. Each reaction exhibits distinct features regarding activity and chemoselectivity. The best catalyst and reaction conditions found were remarkably different for each of the reactions. For one of the reactions, larger-scale studies are presented, which show that the screening reactions provided a fast and reliable indicator of the most promising reaction conditions.

Introduction

The introduction of nitro groups and their (catalytic) hydrogenation is a useful route for the industrial production of amines.[1] Therefore, nitro compounds are frequently used in the synthesis of pharmaceuticals, for instance in the synthesis of sildenafil (Viagra),[2] the antibiotic linezolid (Zyvox),[3] and the HIV protease inhibitor amprenavir (Agenerase)[4] (Scheme 1).

The most frequently used nitro-group hydrogenation catalysts are palladium or platinum on carbon and Raney nickel.[5−7] The hydrogenation of aromatic nitro groups can be performed easily under mild conditions, while hydrogenation of aliphatic nitro groups is usually slower, requiring slightly elevated temperatures and pressures. Hydrogenations of aromatic nitro compounds have been frequently studied, and the reaction pathway is well-known (Scheme 2).[5,7]

In these reactions, the nitroso compound and the hydroxylamine have been observed as intermediates, while a series of side reactions might lead to the formation of hydrazo compounds, which can sometimes also be isolated. The hydrogenation of aliphatic nitro compounds might additionally result in the formation of an oxime, imine, and dimeric amine products (Scheme 3).[7]

In general, the activity and selectivity of this reaction depends on the catalysts as well on the reaction conditions.[8] Indeed, one of the intermediates or side products may become the dominant product; for instance, azoxy, hydrazo, and hydroxylamines can be obtained in high yields.[5,7,9] The accumulation of hydroxylamines is dangerous, as these compounds are thermodynamically unstable.[10] This accumulation may be diminished by using iron- or vanadium-modified catalysts, by using vanadium-based additives,[6,11,12] or by optimizing the reaction conditions.[10]

Chemoselectivity may be an issue in the hydrogenation of more complex molecules. The selectivity in these reactions is influenced by various factors such as the catalyst, the presence of additives, and the reaction conditions.[1,5,7,9]

In this article, we investigate the selective reduction of nitro groups, in the presence of other functional groups, in three pharmaceutical intermediates (Scheme 4). The various catalysts, solvents, and additives that have been used in the three studies are shown in Figure 1. Our philosophy is to fish in the right place and cast as broad a net as possible;

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(1) Downing, R. S.; Kunkeler, P. J.; Van Bekkum, H. *Catal. Today* **1997**, *37*, 121.
(2) Dale, D. J.; Dunn, P. J.; Golighty, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.
(3) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
(4) Al-Farhan, E.; Deininger, D. D.; McGhie, S.; O′Callaghan, J.; Robertson, M. S.; Rodgers, K.; Rout, S. J.; Singh, H.; Tung, R. D. PCT Int. Appl. WO99/48885, 1999.
(5) Augustine, R. L. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1996.
(6) Auer, E.; Berweiler, M.; Gross, M.; Pietsch, J.; Ostgard, D.; Panster, P. In *Catalysis of Organic Reactions*; Ford, M. E., Ed.; Marcel Dekker: New York, 2000; Vol. 82, p 293.
(7) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: New York, 2001.
(8) Dubois, V.; Jannes, G.; Dallons, J. L.; Van Geysel, A. In *Catalysis of Organic Reactions*; Ford, M. E., Ed.; Marcel Dekker: New York, 1994; Vol. 82, p 1.
(9) Figueras, F.; Coq, B. *J. Mol. Catal. A* **2001**, *173*, 223.
(10) Rains, R. K.; Lambers, E. A.; Genetti, R. A. In *Catalysis of Organic Reactions*; Malz, R. E., Ed.; Marcel Dekker: New York, 1996; Vol. 68, p 43.
(11) Baumeister, P.; Studer, M. PCT Int. Appl. WO96/36597, 1996.
(12) Baumeister, P.; Blaser, H.-U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219.

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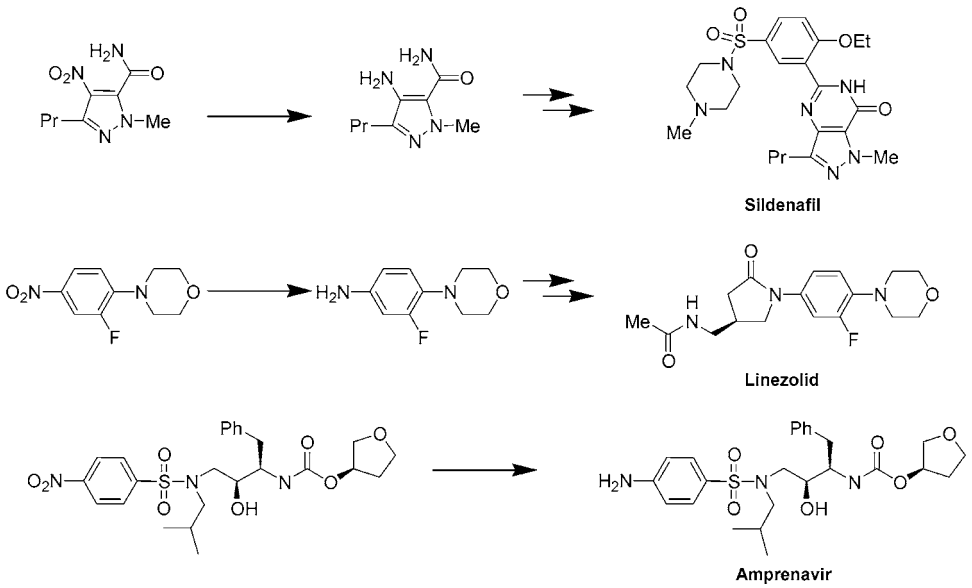
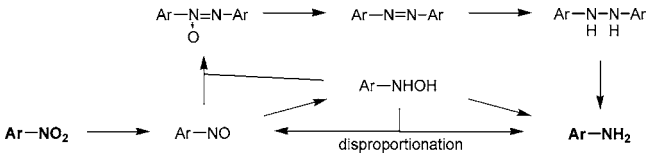
Scheme 1. **Examples of nitro-compound hydrogenations in the synthesis of pharmaceuticals**



Scheme 2. **Hydrogenation of an aromatic nitro compound**



we triangulate on the basis of internal experience, literature precedents, and for catalysts, also on the recommendation of experts from the various suppliers. Full factorial designs were used for all reactions, as variable interactions of the categorical variables (catalyst, solvent, additive) might not have been observed if reduced designs would have been applied.[13] We have used commercial heterogeneous catalysts to allow rapid implementation of "the hits". The large-scale results of one of the hydrogenations is presented.

Experimental Approach

The screening of a reduction step in the synthesis of a multifunctional nitro-containing substrate can be very challenging and time-consuming, considering all the parameters that can be varied.[14] The traditional approach of individual optimization of these variables requires a lot of time. A significant increase in the diversity and number of parameters studied can be achieved by application of high-throughput experimentation techniques (HTE) and in a much shorter time frame than that by traditional methods.[15,16] In fact each study was performed in only a few weeks, from technical closure to final report.

All programs consisted of 264 reactions, involving a screening phase and a small optimization phase. The previously described High-Pressure Units[16] (HPUs) as well as the new Quick Screen (QS) workstation (Figure 2) were used for these studies. The HPUs, comprising 24 reactors, are suitable for the screening of reactions to 30 bar (420 psi) and 150 °C. Avantium's QS workstation can contain up to 16 sets of 12 parallel reactors giving a capacity of 192 parallel reactions. Moreover, a glovebox workflow with automated solids and liquid handling allows for a strictly inert atmosphere. The reactors are fitted with PTFE inserts, and the contents are magnetically stirred. The QS unit has a temperature range of −25 to 150 °C and a maximum pressure of 20 bar (280 psi).

In these screens the workhorse analytical method was HPLC chromatography, using an external standard. The results were clarified by LC−MS on selected samples, to identify the side products, and complemented by NMR spectra to confirm the most promising results.

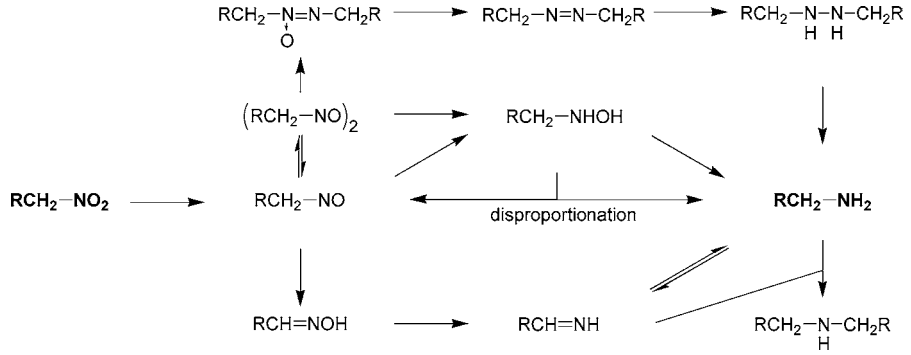
In addition to executing the high-throughput experiments and running the analytical methods, generating and handling large amounts of data are very demanding. Calculation, collection, and visualization of data with, for instance, Spotfire and Avantium's Data Analysis Package (DAPWORKS), contributed to a large extent to the rapid identification of promising catalysts and reaction conditions. For example, an overview of experimental results from all three studies, representing a total of 792 experiments, is shown in Figure 3. This figure clearly shows the reaction profiles with respect to the conversion and selectivity.

Results and Discussion

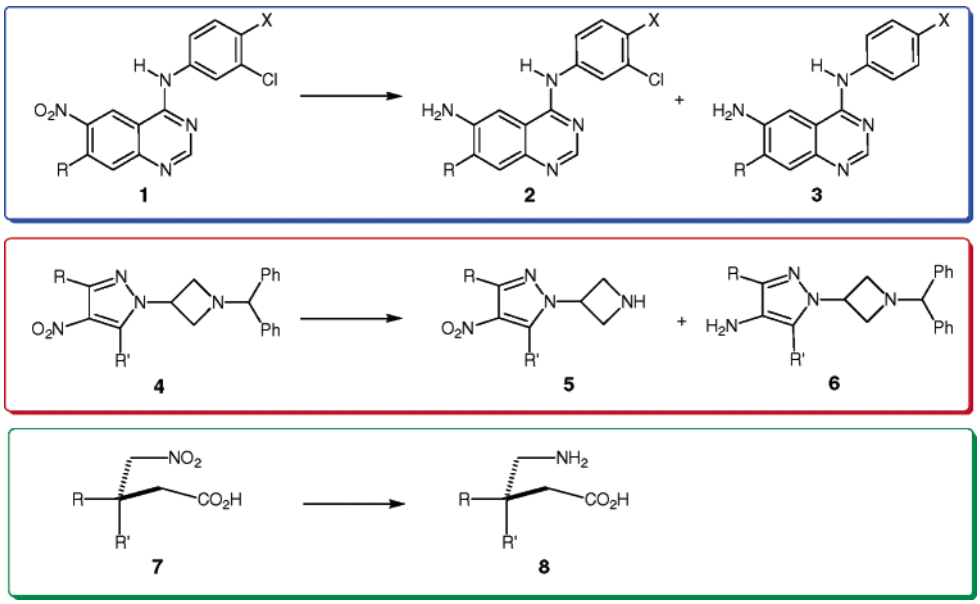
Hydrogenation of a Nitro Group in the Presence of an Aryl Halide. In the original process, the hydrogenation of the aromatic nitro compound **1** was performed with a

(13) McKay, B.; Hoogenraad, M.; Damen, E. W. P.; Smith, A. A. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 966.
(14) See, for example: Watson, T. J.; Horgan, S. W.; Shah, R. S.; Farr, R. A.; Schnettler, R. A.; Nevill, C. R.; Weiberth, F. J.; Huber, E. W.; Baron, B. M.; Webster, M. E.; Mishra, R. K.; Harrison, B. L.; Nyce, P. L.; Rand, C. L.; Goralski, C. T. *Org. Process Res. Dev.* **2000**, *4*, 477.
(15) Special Feature Section: Laboratory Automation in Process R&D. *Org. Process Res. Dev.* **2001**, *5*, 272−339.
(16) Ten Brink, G.-J.; Arends, I. W. C. E.; Hoogenraad, M.; Verspui, G. A.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 497.
(17) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; Wiley: New York, 1991.
(18) Caution: dry, reduced palladium and platinum on carbon are pyrophoric; ignition can easily occur in combination with methanol and air; see: *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Bretherick, L., Urben, P. G., Pitt, M. J., Eds.; Butterworth-Heineman: Oxford, 1999.

Scheme 3. **Hydrogenation of an aliphatic nitro compound**



Scheme 4. **Hydrogenation reactions of the nitro-containing compounds**



Raney nickel catalyst in THF at 90 °C and 3.5−6.5 bar H_2. The reaction resulted in formation of the desired product **2** as well as a significant amount of the deschloro side product **3** (Scheme 4). High levels of the deschloro byproduct were controlled via hot filtration during the workup. The objectives of this study were the minimization of the deschloro side product **3** combined with a high yield of **2**. Less than 0.3% of the side product **3** in the crude reaction mixture would translate to an acceptable level in the isolated product directly, thus avoiding the need for a hot filtration.

Dehalogenation during the hydrogenation of halonitroaromatic compounds is a well-known side reaction. The common nitro hydrogenation catalysts, especially Pd/C, can also effectively be employed as dehalogenation catalysts.[5,7] The ease of dehalogenation depends on the nature of the halogen (I > Br > Cl > F) and its position (ortho > para > meta) relative to the nitro group. It has been reported that the amount of dehalogenated side product can be minimized by optimization of the catalyst and reaction conditions and by the use of additives such as inorganic/organic bases, triphenyl phosphite, or hypophosphorous acid.[5,7]

The experimental scope involved screening a wide variety of 16 heterogeneous catalysts, 5 solvents and 3 additives. The substrate **1** was very soluble in aprotic solvents with a medium polarity. Of these solvents, DME, ethyl acetate (EtOAc), and THF were initially selected, while at a later stage dioxane and 2-methyltetrahydrofuran were also studied. Of the additives known to decrease dehalogenation, magnesium oxide, triphenyl phosphite, and morpholine were selected for this study.[5,7]

From the experimental results, the most important parameters for the hydrogenation of **1** were the catalyst and additive, while no clear distinction was observed between the various solvents. Three different performance levels for the catalysts were apparent:

(1) only low conversions were observed with the metal oxides and the rhodium and ruthenium catalysts;

(2) significant amounts of both product **2** and the deschloro compound **3** were obtained when using one of the palladium catalysts;

(3) the most promising catalysts from the initial screening were 5% Ir/C, various platinum catalysts, and Raney nickel, resulting in large amounts of **2** and only little side product **3**.

The use of these catalysts resulted in high yields of **2** with minimal dechlorination. In some reactions, small amounts of the intermediate hydroxylamine were observed as well. Compared with the results after 4 h, generally higher conversions were observed after 20 h, but the increased

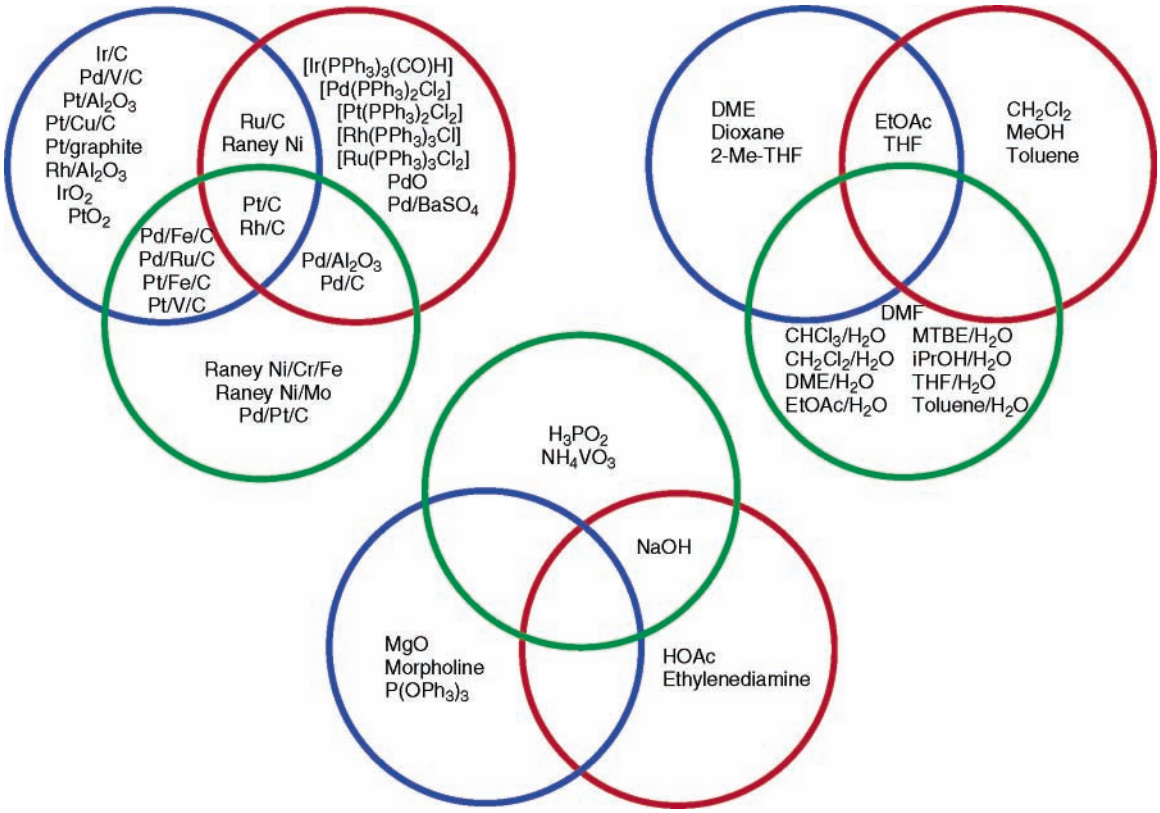


Figure 1. **Ven diagram of all catalysts, solvents, and additives used in the three studies; the colors refer to the respective reactions shown in Scheme 4 (different metal loadings, support properties, and suppliers of the catalysts have not been represented).**

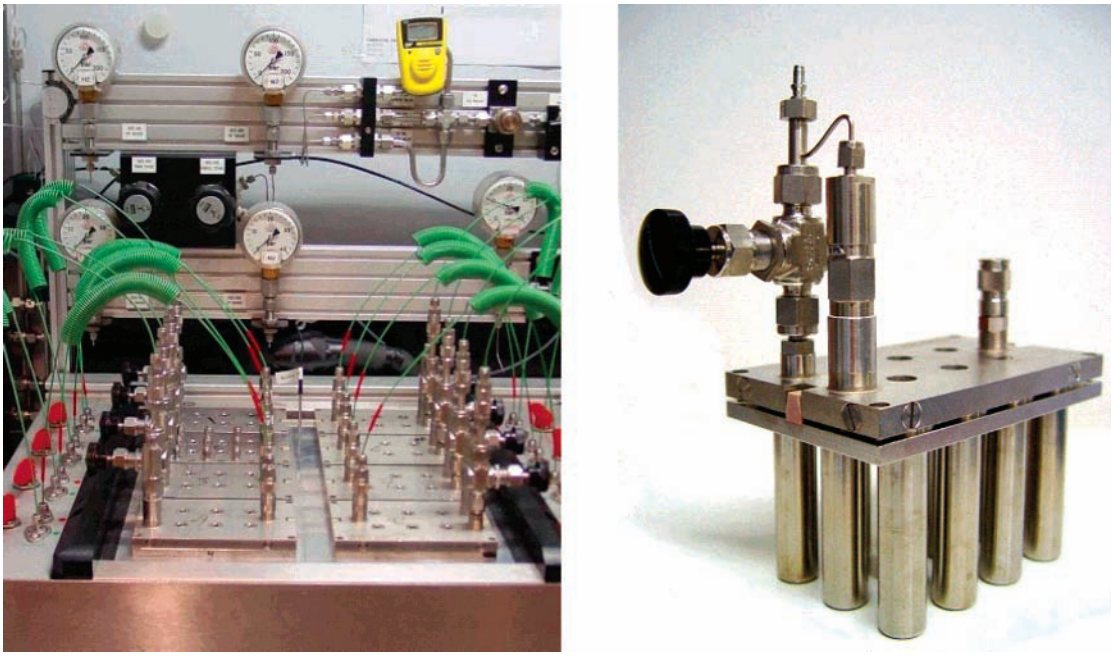


Figure 2. **QS workstation (left), and detail of reactor block (right).**

reaction time usually resulted in lower yields of the hydroxylamine and product **2** in combination with a higher yield of the deschloro compound **3**.

In general, a significant improvement was obtained by the use of an additive, although there are some notable exceptions to this. In Figure 4, some examples are given of the additive effect on the yield of product **2** and the formation of by-product **3**.

As can be observed, triphenyl phosphite was the most effective additive under a range of conditions. With most catalyst and solvent combinations, the use of triphenyl phosphite prevented the formation of the deschloro compound **3**. However, for the most active and selective catalysts, the use of triphenyl phosphite increased the reaction time necessary for a complete hydrogenation. The effects of magnesium oxide and morpholine were also positive, but usually

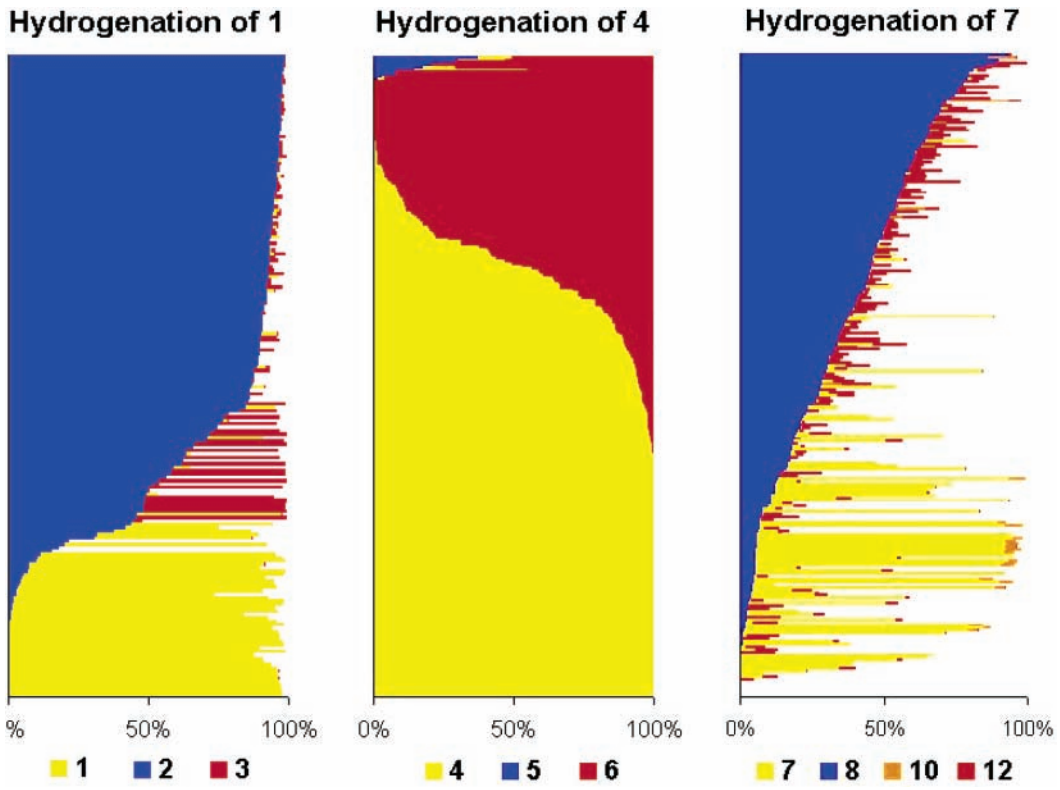


Figure 3. **Overview of the results for all performed nitro hydrogenation reactions (by weight/weight analysis).**

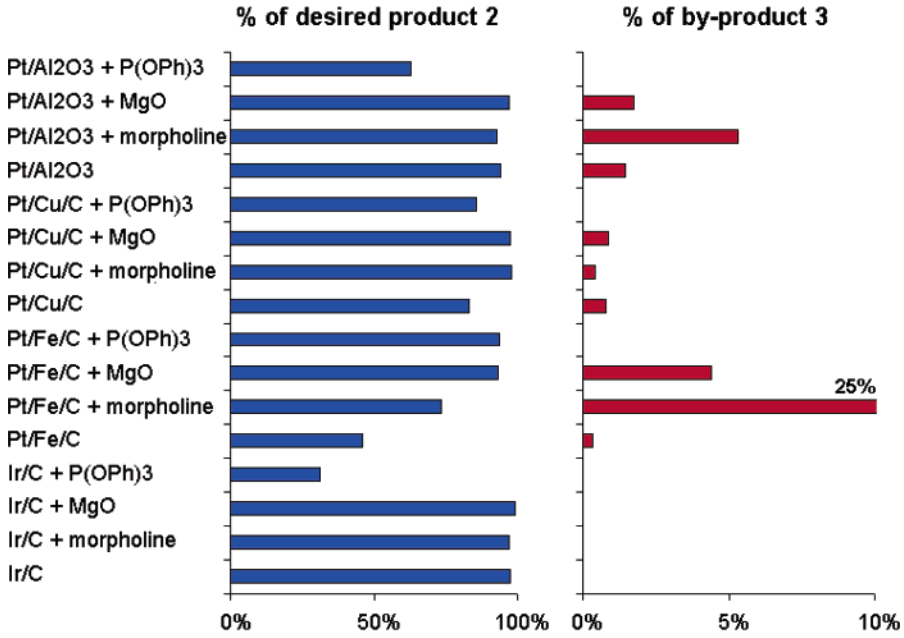


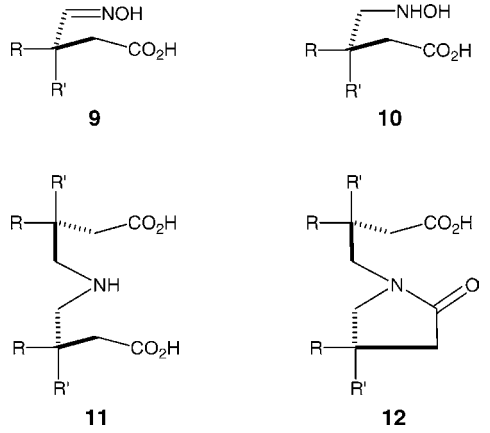
Figure 4. **Additive effect on the yield of product 2 and deschloro by-product 3 after 4 h in THF.**

less pronounced than triphenyl phosphite. In some reactions with morpholine, even a significant increase in dechlorination was observed.

The use of Ir/C generally resulted in the highest yields of product **2** combined with the low amounts of side product **3**. The best result was obtained with Ir/C in THF in the presence of magnesium oxide, resulting in a yield of 99% of product **2** and no deschloro side product **3**, which clearly met the objectives of this study.

Hydrogenolysis of an *N*-Benzhydryl Protection Group in the Presence of a Nitro Group. The aromatic nitro compound **4** and its debenzhydrylated analogue **5** are intermediates in the synthesis of a pharmaceutical compound. Benzhydryl groups and the related benzyl and trityl groups are common protecting groups for amines. Various methods for deprotection are known, including oxidative methods, acid hydrolysis, the use of Na/NH_3, and catalytic hydrogenolysis using palladium or platinum catalysts.[5,17] The

Chart 1. **Observed side products in the hydrogenation of 7**



selective hydrogenolysis of substrate **4** would provide an efficient route to product **5**. However, palladium or platinum catalysts are also commonly used for the hydrogenation of nitro groups. The identification of a catalyst and reaction conditions which allowed selective hydrogenolysis of substrate **4** to product **5** was therefore the objective of this study.

A sample of 13 heterogeneous and homogeneous catalysts were selected for this study. Five solvents were included in the screening: MeOH,[18] EtOAc, dichloromethane, THF, and toluene. One acidic and two alkaline additives were included in this screen as the rate of the *N*-benzhydryl group hydrogenolysis might depend on the acidity of the solution.

In some reactions, the desired product **5** has indeed been observed, notably with 5% Pd/Al_2O_3 in THF and toluene, and in some reactions with 5% $Pd/BaSO_4$ and 5% Pd/C in the presence of additives. However, the amount of product was low, and in all cases larger amounts of the side product **6** were observed. This side product was easily obtained in various reactions with disappointingly high selectivity; conversion from substrate **4** to side product **6** was obtained with Pd/Al_2O_3, Pd/C, Pt/C, and Rh/C in various solvents, and with 5% $Pd/BaSO_4$ in methanol. The highest conversions to side product **6** were generally observed in the more polar solvents. For some catalyst−solvent combinations, the use of an alkaline additive seems to increase the side reaction giving **6**, but no general additive effect could be observed. No significant conversion of the substrate has been observed with Ru/C and any of the homogeneous catalysts, not even after a prolonged reaction time.

These results show that, as expected, the nitro group is more easily reduced compared with hydrogenolysis of the benzhydryl group. The key message from the screen was that by performing a comprehensive search, a rapid route synthesis decision could be made. This route was closed.

Hydrogenation of an Aliphatic Nitro Group. The hydrogenation of the aliphatic nitro compound **7** to the amino acid **8** (Scheme 4) originally resulted in a yield of only 40%. In this reaction, which was performed with a 10% Pd/C catalyst in THF/water (1:1) at 25 °C and 11 bar H_2 (154 psi), various side products were observed. The side products ranged from reaction intermediates (oxime **9** and hydroxylamine **10**) to the dimer **11** and the lactam **12** (Chart 1). The

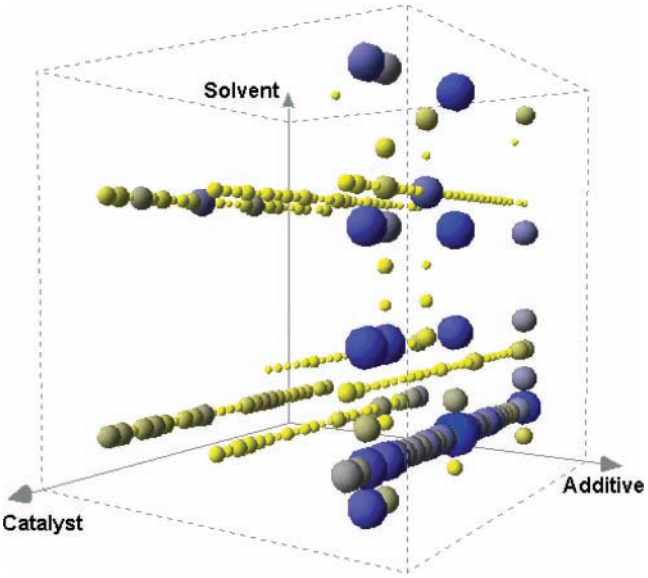


Figure 5. **Representation of all hydrogenation reactions of the aliphatic nitro compound 7 as a function of catalyst, solvent, and additive; the yield of product 8 is indicated by size and color from low (small yellow) to high yield (big blue spheres).**

objectives of this study were therefore simply to increase the amount of desired product **8** in combination with a decrease of the side products.

An initial literature survey implied that the accumulation of intermediates **9** and **10**, and the formation of side products **11** and **12**, depended upon the catalysts to large extent; it transpired that this was less important than first thought. Initially, the emphasis of the study was on a wide selection of catalysts, reducing the solvent and additive dimensions accordingly to fit the project budget.

In the screening phase 25 heterogeneous catalysts, 2 additives, and 3 solvents (or solvent combinations) were used. The solvents selected were neat DMF, THF/water (1:1), and CH_2Cl_2/water (1:1). Alcohols and acetic acid were excluded, as it was known that their use resulted in high yields of the amino ester (not shown) and the lactam **12**, respectively.

In the screening phase, it was shown that the use of additives had a retarding effect on the yield of product **8** but the solvent had a significant effect on the conversion and selectivity (see Figure 5). The reactions in DMF resulted mainly in the formation of side products, while in THF/water, generally a mixture of substrate **7**, product **8**, and side products was obtained. The use of CH_2Cl_2/water (1:1) resulted in the highest amounts of desired product. The lactam **12** was the main (and often only) observed side product. The substrate **7** is soluble in most organic solvents, but the product **8**, only in very polar solvents, and hence solvent partitioning could be an important lever on the selectivity of the process. Consequently, the range of biphasic solvent systems was extended in the optimization phase, while reducing the number of catalysts on the basis of the screening results.

In the optimization phase, it was observed that the use of THF/H_2O, $CHCl_3/H_2O$, and DME/H_2O resulted in lower yields of the desired product **8** compared to yields with toluene/H_2O, CH_2Cl_2/H_2O, EtOAc/H_2O, and MTBE/H_2O.

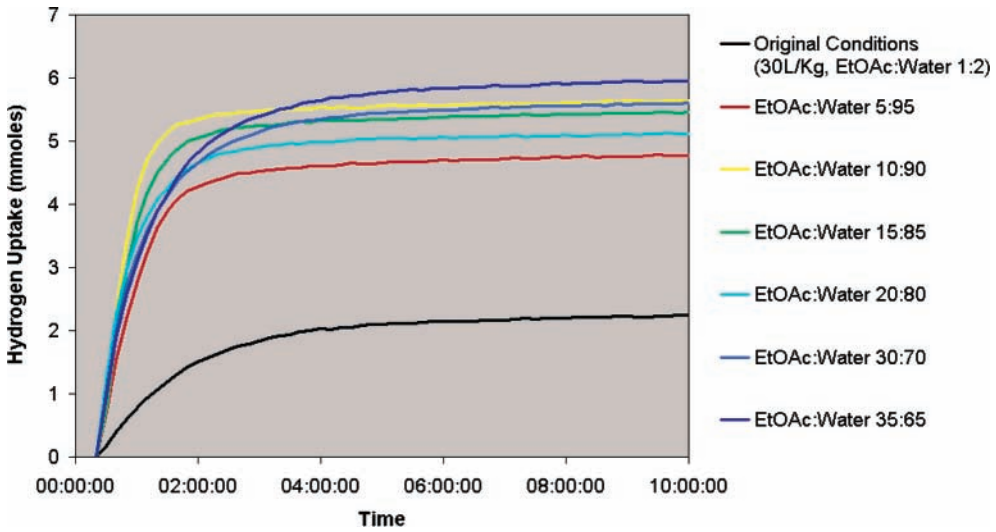


Figure 6. **Solvent screen for the hydrogenation of nitro compound 7.**

The highest yields have been obtained with 5% Pt/C and 5% Rh/C, of which the use of the Pt/C catalyst is slightly favored because it results in lower amounts of the lactam **12**. In general, the lowest amounts of this side product relative to that of the product **8** were obtained with Raney nickel (Mo modified), while the palladium-containing catalysts gave the highest relative amounts of the lactamised dimer **12**.

In Figure 5, an overview of all hydrogenation reactions of compound **7** is shown, in which the screening phase (series of data points) and optimization phase (individual data points) can be clearly distinguished.

Apart from the solvent and type of metal, the yield of product **8** is significantly influenced by the catalyst support and the amount of substrate. High yields have been obtained with a 5% Pt/C catalyst with a neutral-to-basic support. The use of similar catalysts, but with an acidic support, resulted in a much lower yield and more side products. An increase in the formation of the lactam **12** was also observed when the substrate concentration was increased from ca. 50 to 100 mg/mL, resulting in a change of the product-to-lactam ratio from ca. 10:1 to 10:4.

The increased formation of the lactam **12** at higher substrate concentrations indicates that a high (local) concentration of the reaction intermediates and product **8** in the same (organic) phase should be avoided. This is probably also accomplished by the change from THF/water to a system with water and a water-immiscible organic solvent. In the latter solvent combinations, the hydrogenation of the substrate **7** to product **8** occurs in the organic phase. Subsequently, the product accumulates in the aqueous phase (probably as zwitterion) and does not react further. The successful combination of such a biphasic solvent system and a suitable catalyst resulted in an increase in the yield of product **8** from the original 40% to more than 90% and underpinned the larger-scale studies described in the next section.

Large-Scale Studies of the Hydrogenation of 7. The most promising results of the HTE screening study have been investigated on a larger scale. In these studies, the Pt/C catalysts proved to be slightly superior when compared with other catalysts selected from the screening phase. In 1-L scale reactions, the crude product **8** was isolated by phase separation and evaporation of the aqueous phase. A high yield of 90% was obtained, which is similar to the best results obtained during the screening reactions. The reaction was scaled up; workup involved separation, concentration of the aqueous phase, and slow addition of 2-propanol to crystallize, affording the purified product **8** in 68% yield.

Table 1. **Effect of EtOAc-to-water ratio on the yield of product 8**[a]

solvent system	yield (%)
EtOAc:water 5:95	75
EtOAc:water 10:90	86
EtOAc:water 15:85	95
EtOAc:water 20:80	98
EtOAc:water 25:75	98
EtOAc:water 30:70	100
EtOAc:water 35:65	99
EtOAc:water 33:67 (control, 30 L/kg)	97

[a] Concentrations of 10 L/kg; yields determined as main band area by ELSD; reaction mixtures were diluted with acetonitrile (5 mL) to give single-phase solutions for HPLC analysis.

One of the key issues which detracted from the above procedure as an attractive plant process was the large volumes of solvent used. We were keen to investigate the effect of lowering the total reaction volume but recognized that precipitation of the product amino acid during the course of the reaction may be a problem. To this end, seven different ratios of ethyl acetate to water were investigated, using an Argonaut Endeavor platform. All experiments were performed on a 0.5-g scale at 10 L/kg, a 67% reduction in solvent volume. An eighth control experiment was included, being a repeat of the 1-L scale reactions described above, but now carried out on a 0.1-g scale. The results of these experiments are shown in Figure 6 and Table 1.

A decrease in the amount of ethyl acetate to 10% increases the rate of reaction. However, if the level of ethyl acetate is dropped even lower (as low as 5%), then the reaction rate is

significantly affected; it slowed the reaction and increased the level of impurities. Therefore, the conditions that utilized 15% ethyl acetate and resulted in a yield of 95% are being considered for further scale-up of this reaction.

Conclusions

The hydrogenation of a multifunctional pharmaceutical substrate containing a nitro group is very challenging. In one case a route selection choice was made on the basis of the results from the high-throughput screening; the route was quickly discarded. For the other two reactions involving the nitro group reduction that are presented in this contribution, the screening studies allowed rapid identification of promising catalysts and reaction conditions. The ideal catalysts and reaction conditions clearly depend on the properties of substrate and product as well as on the process requirements. This is illustrated in the hydrogenation of the aliphatic nitro compound **7** to the amino acid **8**. For this reaction, an increase in the yield from 40 to 90% was obtained as a result of the high-throughput studies; these results were confirmed at a 1-L scale. Further optimization of the solvent composition resulted in a process that is promising for future production-scale synthesis.

Experimental Section

Large-Scale Hydrogenation of 7 with Isolation of Crude. The aliphatic nitro compound **7** (33.4 g) was dissolved in ethyl acetate (0.34 L), and demineralized water (0.68 L) was added. The two-phase mixture was charged to an autoclave, and the catalyst (5% Pt/C 50% wet, Degussa F101, 6.7 g) was added. After purging with N_2 and H_2 the reaction mixture was heated to 50 °C and hydrogenated at 11 bar (154 psi) for 24 h. The autoclave was purged with N_2 and heated to 70 °C; the reaction mixture was then filtered to remove the catalyst. The two phases were separated at 70 °C, and the upper organic layer was discarded. The aqueous phase was allowed to cool and was then concentrated in vacuo, providing the product **8** as white solid in 90% yield (25.9 g).

Telescoped with Crystallization Process. The aliphatic nitro compound **7** (34.1 g) was dissolved in ethyl acetate (0.34 L), and demineralized water (0.68 L) was added. The two-phase mixture was charged to an autoclave, and the catalyst (5% Pt/C 50% wet, Degussa F101, 6.9 g) was added. After purging with N_2 and H_2 the reaction mixture was heated to 50 °C and hydrogenated at 11 bar (154 psi) for 24 h. The autoclave was purged with N_2 and heated to 70 °C; the reaction mixture was then filtered through Celite to remove the catalyst. The damp cake containing the catalyst was washed with demineralized water (0.02 L). The two phases were separated at 70 °C, and the upper organic layer was discarded. The aqueous phase was reduced in volume by distillation at atmospheric pressure (0.64 L water removed). The aqueous solution was cooled to 40 °C at which point precipitation occurred, and then 2-propanol (0.71 L) was added at 40 °C over 10 min. The white suspension was then cooled from 40 to 5 °C over 40 min, at which point the slurry was stirred for 60 min. The suspension was filtered, and the damp cake was washed with 2-propanol (0.04 L). The white crystalline solid was dried in vacuo at 40 °C to give the product **8** in 68% yield (19.9 g).

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