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Catalytic Hydrogenation of Cyanohydrin Esters as a Novel Approach to *N*-Acylated β-Amino Alcohols – Reaction Optimisation by a Design of Experiment Approach

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The catalytic hydrogenation of acylated cyanohydrins and subsequent intramolecular migration of the acyl group to yield pharmaceutically interesting *N*-acyl β-amino alcohols is shown to be a successful one-pot preparation method. The combination of a multistep DoE approach and high-throughput methodology proved to be an effective strategy for the optimisation of the reaction. With the favoured catalyst/solvent combination of nickel on alumina in dioxane, both hydrogenation and acyl group migration proceeded smoothly, giving the *N*-acyl β-amino alcohols in yields (determined by GC) of up to 90 % for aliphatic substrates and up to 50 % for benzylic ones, the latter being more prone to side reactions. No racemisation was found to occur at the chiral centre of an aliphatic molecule when an enantiopure cyanohydrin ester was used, though a minor decrease in *ee* was observed with a benzylic substrate.

Introduction

N-Acylated β-amino alcohols such as aegeline (see Figure 1) occur in nature and can readily be converted into β-*sec*-amino alcohols, an important class of compounds in the pharmaceutical and agrochemical industries. Some representative examples of the numerous biologically active β-*sec*-amino alcohols are etilefrine, bamethane and denopamine (Figure 1). An established route to *N*-acyl β-amino alcohols is by the reduction of the free cyanohydrin, followed by acylation of the amino group.[1] The reduction is usually performed by use of stoichiometric amounts of either $LiAlH_4$ or BH_3, but it can also be achieved by catalytic hydrogenation under strongly acidic conditions.[2] If enantiopure substrates are used, the stereocentre remains intact during all these reactions. Given the low atom efficiency of aluminium and boron hydride reductions, and the strongly acidic conditions required for the catalytic hydrogenations, a different approach has been investigated, with the overall aim of integrating the reduction and acylation steps in a one-pot procedure under mild conditions.

The unprotected cyanohydrins commonly used as starting materials are relatively unstable and racemise easily. In contrast to this, cyanohydrin esters are stable and do not racemise. Moreover, they are readily prepared, both in their racemic[3] and in their enantiopure forms.[4] In addition, the acyl group of a protected cyanohydrin is a potential intramolecular acyl donor (see Scheme 1). After the catalytic hydrogenation of the nitrile group, the newly formed amine, as a strong nucleophile, can immediately react with the neighbouring acyl group via a five-membered transition state to yield the *N*-acyl β-amino alcohol. This type of intramolecular acyl migration has previously been described in the $NaBH_3(OCOCF_3)$ reduction of an acylated cyanohydrin to yield denopamine,[5] suggesting that it should proceed equally well after catalytic hydrogenation of the nitrile.

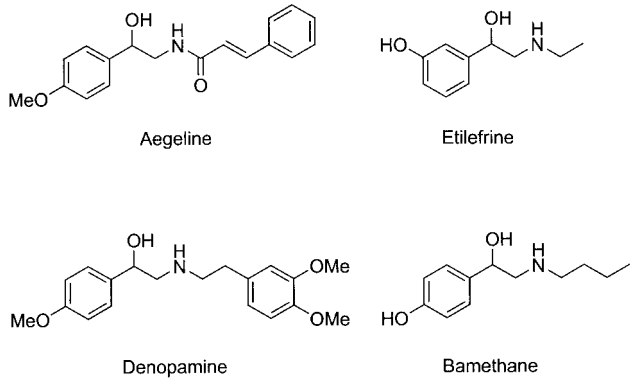

Figure 1. *N*-Acyl-β-amino alcohols and β-*sec*-amino alcohols showing high biological activity.

Earlier reports of catalytic hydrogenations of acylated cyanohydrins, and in particular of mandelonitrile esters, describe the application of Pd/C or PtO_2 under strongly acidic conditions.[6] The primary products obtained were not the *N*-acyl β-amino alcohols but β-phenyl ethylamines, owing to the facile hydrogenation of benzylic C–O bonds over platinum or palladium catalysts. In this case the amine was the desired product.[6a] In the current work, however, the

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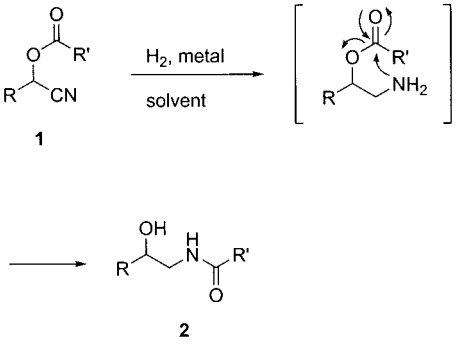


Scheme 1. The hydrogenation of acylated cyanohydrins with subsequent acyl migration.

objective is to maximize the yields of the *N*-acylated β-amino alcohols, and the reductive cleavage of the benzylic C–O bonds needs to be avoided. This investigation of a selective, catalytic route for the direct conversion of acylated cyanohydrins (**1**) into *N*-acylated β-amino alcohols (**2**) employed high-throughput methods for the screening of catalysts, solvents and reaction conditions.

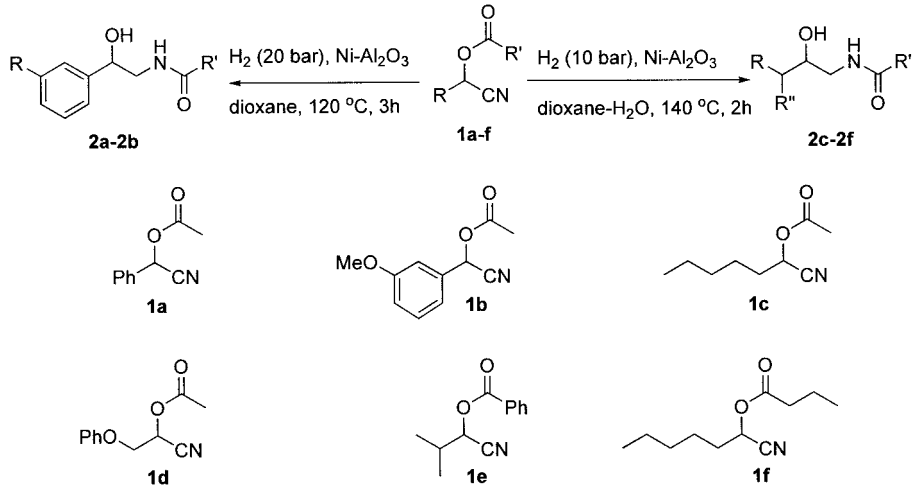
The large number of parameters to be investigated suggested a Design of Experiment (DoE) approach. DoE methodologies[7] are superior to traditional methods involving the consecutive optimization of the various parameters; they make it possible to maximize the amount of information that can be obtained from the results while minimizing the number of experiments, and also increase the likelihood of establishing the true optimum within the search space. The experiments to be performed are chosen statistically in order to cover the whole search space as efficiently as possible. The size of the design (selected number of reactions) depends on the kind of information that is desired. In the present case, a strategy of three sequential small designs was adopted; this enables the information obtained from the first to be used to improve the subsequent designs.[8] Preliminary small designs (typically less than 25% of the possible number of reactions) are sufficient to distinguish between significant and insignificant parameters and are therefore well suited to reduce the search space in the early stages of the research effort. A parameter has a significant effect if it produces a positive or negative change that is above the 95% confidence interval of the variance. Though continuous refinement of the conditions in subsequent optimisation designs, the most influential parameters can then be studied, and further optimisation achieved. Since the number of parameters to be investigated has been reduced, the number of experiments per parameter can be increased. In this way, more information on the main effects, and especially on the interactions of the parameters, can be obtained. In such designs more than 50% of the possible number of reactions are typically performed. Such a sequence of DoEs is believed to be a better strategy than one large one, because the information obtained from one design is used to improve the next.

Results and Discussion

As shown by Hartung,[6a] the hydrogenation of benzylic cyanohydrin acetates easily yields products such as β-phenyl ethylamines through reductive cleavage of benzylic C–O bonds. In an aliphatic substrate, on the other hand, the C–O bond is more stable and resistant to cleavage even under drastic conditions. Different conditions are likely to be required for the selective hydrogenation of aliphatic and benzylic cyanohydrins, so it was decided to optimise the reactions for mandelonitrile acetate (**1a**), representative of benzylic substrates, and 2-cyanohexyl acetate (**1c**; see Scheme 2), representative of the aliphatic substrates, separately.

First Design

The use of a DoE strategy requires as the first step the compilation of all potentially important parameters, based on previous experience, the literature or chemical intuition. The initial search space should be broad enough to assure



Scheme 2. The catalytic hydrogenation of cyanohydrin esters.

that the real optimum of the reaction is included. In the hydrogenation of nitriles the main factor influencing the reaction rate and the product distribution is the metal in the hydrogenation catalyst, with the most commonly used being Raney nickel, Raney cobalt, Pd/C, Pt/C, Ru/C and Rh/C.[9] The same metals supported on SiO_2 and Al_2O_3 are often employed as well.[9] Normally Rh, Pd and Pt tend to give more secondary and tertiary amines than Co, Ni and Ru. As the migration of the acyl group might suppress the formation of secondary and tertiary amines, these metals were also included in the investigation. For the initial screening, Ni, Pd, Rh, Pt and Ru, on carbon and Al_2O_3 as carriers, were selected as representative catalysts.

The solvent is a second important parameter. The most commonly used solvents for the hydrogenation of nitriles are protic solvents such as methanol and ethanol. However, since the envisaged reaction involved acyl group migration, solvents with a broader range of properties were selected: 2-propanol (IPA, a protic solvent but less polar than methanol), dioxane (an aprotic, polar ether) and toluene (a relatively apolar solvent).

It is known that the addition of ammonia and of water can change the distribution ratio of the products of nitrile hydrogenation.[9] Ammonia is a commonly used additive, favouring the formation of primary amines, though in the present case reaction with the ester group is a possible side reaction. Reports on the effect of water are conflicting; several cases have been reported in which water is added to promote the formation of both primary and secondary amines[10] but it has also been claimed that water does not change the product distribution but instead increases the reaction rate.[11] The effects of both these additives were studied in the initial screening.

The parameter space for the initial screen is summarised in Table 1. The reaction temperature was varied over two levels. The small reactors of the high-throughput unit did not permit independent variation in pressure, which was kept constant at 20 bar H_2. A selection of 24 reactions out of the total of 320 possible combinations was made for each of the two substrates by use of a D-Optimal algorithm.[12] This design is sufficient to study the main effects of each parameter, and a subsequent more detailed study would then allow for further optimisation. Acidic conditions were not included, since any formation of the amino salts would prevent the intramolecular migration of the acyl group. Furthermore, in contrast to the free cyanohydrins, the cyanohydrin esters (**1**) are more stable towards possible basic side products such as the secondary amines.

After the execution of the 2×24 reactions, *N*-acyl β-amino alcohols **2a** and **2c** were identified among the products in two of the experiments for each substrate, showing the hydrogenation to have indeed been followed by intramolecular acyl migration in a one-pot procedure. The conditions for the four successful reactions are given in Table 2. The results of the first screening show the advantage of using DoE with successive small designs as an approach towards the optimisation of a new reaction. This made it possible to investigate a large parameter space and to identify the region of interest for further exploration, even though only 8% of the possible number of reactions had been executed. If a single large DoE design had been chosen, a large number of unnecessary reactions would have been performed.

When using such a small design it is important to realise that each result is extremely influential for the calculation of the main effects of the parameters. These calculations will become increasingly inaccurate with a growing number of "zero-yield" reactions or failed experiments. In this case the number of reactions affording the desired product is so low (i.e., 2 per design) that a statistical evaluation of the effect of the parameters on the yield would not be meaningful. The results do, however, enable the identification of unfavourable factors and their exclusion from the next screening phase.

The reactions in Table 2 were all run for 24 hours at 120 °C, with either dioxane or 2-propanol as the solvent and ammonia or water as the additive. The successful metals were Ni and Rh, supported on either carbon or alumina.

Table 1. The parameter space to be investigated for substrates **1a** and **1c**.

Parameter	Level 1	Level 2	Level 3	Level 4	Level 5
Temperature (°C)	90	120	–	–	–
Reaction time (h)	3	24	–	–	–
Support	alumina	carbon	–	–	–
Solvent	2-propanol	toluene	dioxane	methanol	–
Additive	no additive	H_2O	NH_3	$H_2O + NH_3$	–
Metal	Ni	Pd	Pt	Rh	Ru

Table 2. Conditions for the successful hydrogenation in the initial screening.

Substrate	Metal	Support	Temp. [°C]	Solvent	Additive	Conversion[a] of **1** [%]	Yield[a] **2** [%]
1a	Ni	C	120	dioxane	NH_3	100	33
1a	Rh	Al_2O_3	120	dioxane	$NH_3 + H_2O$	100	24
1c	Ni	Al_2O_3	120	dioxane	H_2O	100	65
1c	Rh	C	120	2-propanol	H_2O	100	48

[a] According to GC.

From the reactions that did not yield the desired product, the following trends could be observed: the reactions using Ru or toluene gave low degrees of conversion, while the reactions performed in MeOH in all cases gave complete conversion, but with a wide range of side products. Since the intention of the first screening was to reduce the parameter space, none of the side products of the reactions was isolated. However, GC-MS enabled the identification of several side products (**3** to **6**; Figure 2).

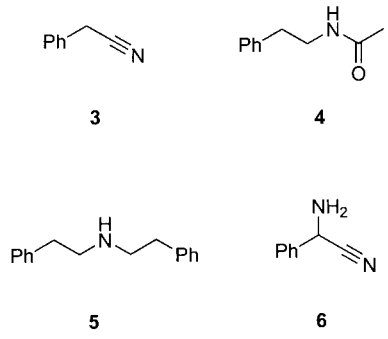


Figure 2. Identified side products in the hydrogenation of **1a**.

The presence of **5** shows that the secondary amine had been formed in some cases. Products **3** to **5**, in which the benzylic alcohol group has been removed, were particularly dominant when platinum was used as the catalyst, which is to be expected from the application of platinum catalysts for the cleavage of this type of bond. Equivalent byproducts could also be identified in the case of the aliphatic substrate, though in much smaller amounts, which is in accordance with the greater stability of the C–O bond. The fact that even the aliphatic C–O bond can be cleaved can be attributed to the stabilising effect of the nitrile group on the intermediate radical formed during the cleavage.

In the successful reactions of **1a** (see Table 2) ammonia was present as additive, but analysis of the results did not show unambiguously that the presence of ammonia was essential. Since the formation of **6** indicates that ammonia also reacts with the substrate it was decided, in order to avoid this side reaction, to optimise the conditions further in the absence of ammonia.

Samples taken after 3 hours showed only low degrees of conversion and there was no formation of **2a** or **2c** in any reaction other than those performed under the conditions reported in Table 2. The long reaction time could be due to an initial activation period for the catalyst but the study of this was deferred to a later stage and a reaction time of 24 h was maintained for the second design.

From the results of the first design, the second was conducted with the parameters indicated in Table 3. In order to study the effect of the carrier further, silica was included in this design. Since the parameter space was now considerably reduced, a full factorial design (i.e., 36 combinations) was now feasible for each substrate. All the reactions were performed at 120 °C and 20 bar H_2, with a reaction time of 24 hours.

Table 3. Conditions and parameters in the second screening round.

Parameter	Level 1	Level 2	Level 3
Additive	no additive	H_2O	–
Solvent	2-propanol	dioxane	–
Metal	Ni	Rh	Ru
Support	alumina	carbon[a]	silica

[a] In the case of nickel, Raney nickel was used instead of nickel on carbon.

The results of this screening are presented in Figure 3 and Figure 4. Conversion of **1a** and **1c** was 100% in all cases, except for those reactions in which Ru–alumina and Ru–silica were used. For those two catalysts no conversion was observed. In sharp contrast to the first screening, in which only a few reactions had yielded the *N*-acyl β-amino alcohols, all active catalysts now yielded the desired products. A statistical evaluation of the results shown in Figure 3 and Figure 4, with respect to the significance of the main effects of the parameters and their interactions, is presented in Figure 5 and Figure 6.

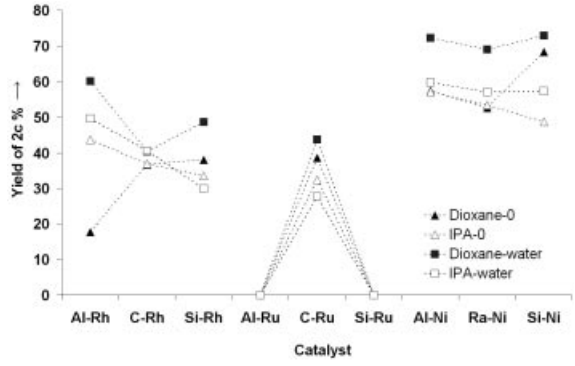


Figure 3. Graphical representation of the results of the second screening with substrate **1c**.

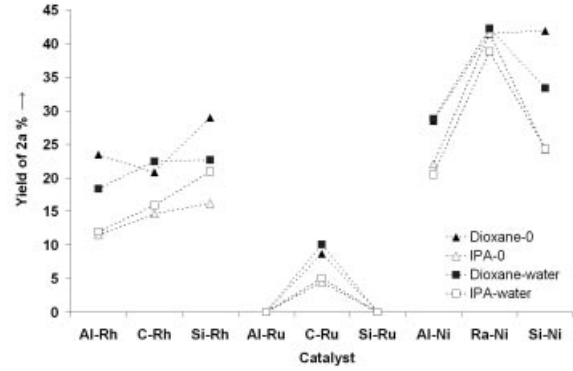


Figure 4. Graphical representation of the results of the second screening with substrate **1a**.

In the evaluation of the main parameters in Figure 5, many similarities for the two different substrates can be noted. The most important parameter in both cases is the type of metal, with nickel being the best, followed by rhodium. For ruthenium, the poor results from the initial

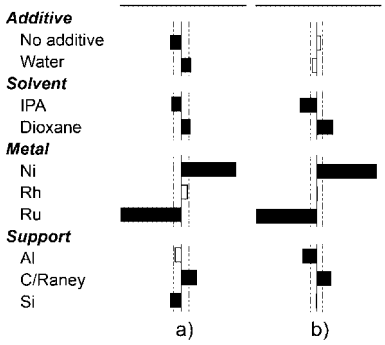


Figure 5. Effect of the main parameters in the second screening: a) aliphatic substrate **1c**, b) benzylic substrate **1a**. The lengths of the bars show the relative influence of the main parameters on the yields of **2a** and **2c**. The bars directed to the right have a positive relative effect and those to the left a negative one. The dotted lines represent the 95% confidence interval calculated from the estimated experimental variance. Effects higher than this confidence interval are considered significant and are represented in black ("Al" = alumina, "Si" = silica).

screening are confirmed. In the initial screening, the successful reactions included those in which water had been used as an additive. A small but statistically significant positive effect of water is indeed observed in the case of the aliphatic substrate, though not with the benzylic one. Although the difference between the two solvents is small, dioxane is statistically significantly better than 2-propanol for both substrates. With respect to the effects of the catalyst carriers, the apparent superiority of carbon is a function solely of the fact that ruthenium gives the product only in combination with carbon while, in addition, nickel on carbon was not available and Raney-Ni was used instead, so no conclusions on carrier effects can be drawn from this second design.

With respect to the interactions between the parameters shown in Figure 6 it was noted that, for both substrates, there are significant additive/solvent and metal/support interactions, while in the case of the benzylic substrate a solvent/metal interaction also exists. However, the effects of these interactions are relatively small in comparison with the main effect of the metal itself. For the aliphatic substrates, nickel on silica, in dioxane as the solvent and with water as additive, is the combination of choice, while for the benzylic substrate Raney nickel is the indicated catalyst, in dioxane without addition of water.

All the reactions from these two screenings were performed on the "Quick Catalyst Screening 96" platform. This equipment has a maximum pressure limit of 20 bar and no individual temperature control for the reactors. Further optimisation of pressure and temperature was for that reason performed in a conventional autoclave.

In preparation for this, a test was conducted to determine whether the results obtained with the nickel catalysts could be improved by activation with H_2 prior to the catalytic test. After activation of the catalysts at 140 °C for 12 hours at 40 bar H_2, nickel on alumina gave similar yields to those of Raney nickel and nickel on silica and it was found conve-

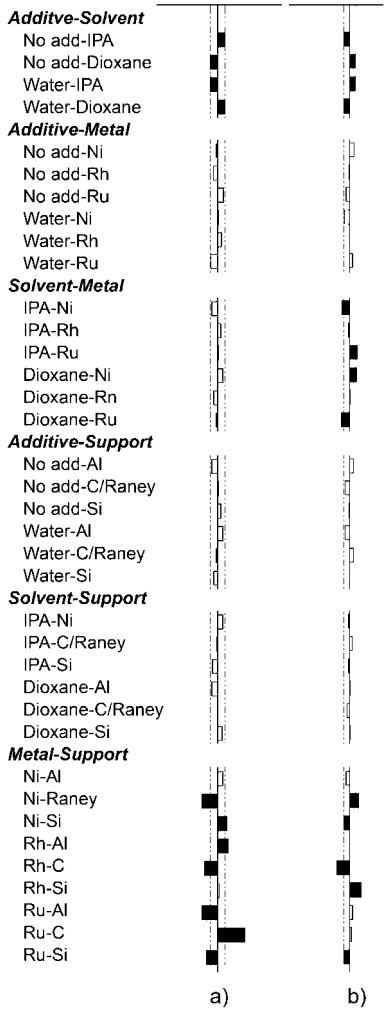


Figure 6. Interaction effects between the parameters of the second screening: a) aliphatic substrate **1c**, b) benzylic substrate **1a**. The lengths of the bars show the relative influence of the interaction effects, between the different parameters, on the yields of **2a** and **2c**. The bars directed to the right have a positive relative effect and to the left a negative one. The dotted lines represent the 95% confidence interval calculated from the estimated experimental variance. Effects higher than this confidence interval are considered significant and are represented in black ("Al" = alumina, "Si" = silica).

nient to use this catalyst for further optimisation. In the case of the aliphatic substrate the reaction time was reduced to two hours, and for the benzylic substrate to three hours. Once again, dioxane proved to be slightly superior to 2-propanol As a result of this, it was decided to perform the third round of screening, for the optimisation of temperature and pressure, with activated nickel on alumina in dioxane. In the case of the aliphatic substrate **1c**, water was used as an additive.

Third Design

A temperature range of 80 to 160 °C and a pressure range from 5 to 40 bar were tested. Only minor differences in the yield (±7% for the aliphatic, ±5% for the aromatic)

Table 4. Degrees of conversion and yields from the hydrogenation of acylated cyanohydrins **1a**–**f**.

Substrate	Conversion of **1** [%]	NMR yield of **2** [%]	Isolated yields of **2** [%]
1a	100	n.d.	49[a]
1b	100	n.d.	50[a]
1c	100	74	57[b]
1d	100	91	72[a]
1e	100	≈ 75	58[a]
1f	100	83	30[b]

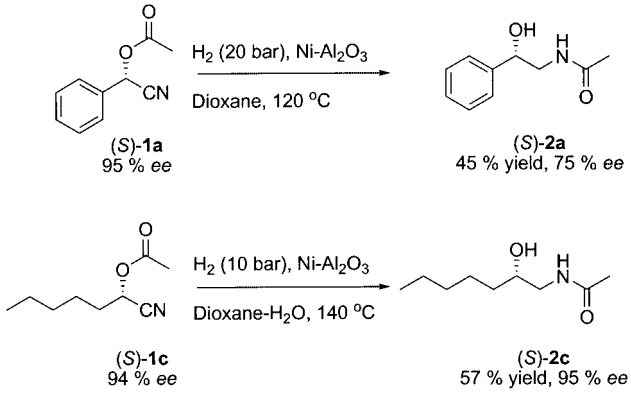
[a] Isolated by column chromatography. [b] Isolated by recrystallisation from ethyl acetate, yield not optimised.

were observed, except for reaction temperatures below 90 °C, at which hardly any reaction occurred. Despite the small differences in the observed yields an optimum of 10 bar H_2 at 140 °C was found for the aliphatic substrate **1c**, whilst 20 bar H_2 at 120 °C was found for the benzylic substrate **1a**.

Other Substrates

In order to establish the versatility of the reaction, these optimised conditions were applied to a number of other acylated cyanohydrins: a substituted benzylic ester (**1b**), an aliphatic substrate with an aromatic side chain (**1d**) and aliphatic substrates with a variety of acyl groups (**1e**, **1f**) (Scheme 2, Table 4). All these substrates were successfully hydrogenated to yield the desired *N*-acyl β-amino alcohols **2a**–**f**. Substrate conversion was 100% in all cases. The benzylic substrates **1a** and **1b** gave more side products than the aliphatic **1c**–**f**. This difference between the substrates is in accordance with the unstable benzylic C–O bond. In the cases of **1c** and **1f**, the products were isolated from the reaction mixtures by crystallisation.

The hydrogenation was also performed on the optically active substrates (*S*)-**1a** (95% *ee*) and (*S*)-**1c** (94% *ee*). As expected, the chiral centre of (*S*)-**1c** was found to remain unchanged during both the hydrogenation and the intramolecular migration. This was not the case with (*S*)-**1a**, however, and the isolated (*S*)-**2a** had an *ee* of only 75% (see Scheme 3). This decrease in *ee* might be explained by a combination of elevated temperatures and a base-catalysed racemisation of the substrate, the base being either ammonia released in the formation of the secondary amine side product, or the secondary amine itself.



Scheme 3. Catalytic hydrogenation of enantiopure acylated cyanohydrins.

Conclusion

The catalytic hydrogenation of acylated cyanohydrins (**1**) with subsequent intramolecular acyl group migration constitutes a valuable one-pot route to the pharmaceutically important *N*-acyl β-amino alcohols (**2**). Nickel on alumina as catalyst in dioxane as solvent proved to be preferable to the traditional catalysts (Pd/C and PtO_2) used under acidic conditions;[2e] both the hydrogenation and the migration proceeded smoothly and the desired products could be obtained in yields of up to 90% for the aliphatic substrates and up to 50% for the more sensitive benzylic substrates, as determined by GC. Application to a range of aliphatic and aromatic substrates with different acyl groups was demonstrated. Aliphatic substrates not only gave the highest yields but in the case of an enantiopure aliphatic cyanohydrin acetate the stereocentre remained unaltered during the reaction. On the other hand, a small amount of racemisation could be observed for a sensitive enantiopure benzylic substrate. Given the straightforward access to the (chiral) starting materials and the mild, catalytic reaction conditions this one-pot sequence represents a valuable addition to the arsenal of organic chemists.

A multi-step DoE approach proved an efficient method for the optimization of the reaction. Out of more than 2000 possible combinations of the parameters needing to be studied, it proved possible to effect the optimization through the use of only 70 experiments for each substrate. This shows the great advantage of the DoE approach for the optimisation of a new reaction, enabling a large parameter space to be investigated and the most interesting range within the parameter space to be identified.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on Varian VXR-400S (400 and 100 MHz, respectively) or Varian Unity Inova 300 (300 MHz and 75 MHz, respectively) instruments. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quadruplet) and m (multiplet).

Mass spectra were determined on a VG 70 SE spectrometer operating at 70 eV. GC-MS was measured with a VG 250 SE instru-

ment fitted with a CP Sil 8 CB column of 25 m × 0.25 mm and 0.4 μm DF. A Varian Star 3600 GC fitted with a CP Sil 5CB column with 50 m × 0.55 mm and 1 μm DF was used to determine the levels of conversion in the crude reaction mixtures. Optical rotations were obtained with a Perkin–Elmer 241 polarimeter. Melting points are uncorrected. Column chromatography was carried out with silica gel packing of 0.060–0.200 mm, pore diameter ca. 6 nm, with mixtures of petroleum ether (PE), methanol (MeOH) and ethyl acetate (EtOAc) as solvents. TLC was performed on 0.20 mm silica gel. The nickel catalysts were all activated at 140 °C for 12 hours at 40 bar H_2 before use in General Procedures B, C and D described below. All other catalysts, and the solvents employed, were used as received from commercial sources. For all the supported catalysts the metal loading was 5%, except for Rh-silica (1%), Ni-alumina (50%) and Ni-silica (66%). Racemic[3] and enantiopure cyanohydrin acetates[4b,13] were synthesised by literature procedures. The optical purity of **2a** was determined by HPLC with use of a Waters 510 pump, a 4.6 × 250 mm 10 μ Chiracel OJ column and a Waters 486 UV detector. The eluent was a mixture of hexane and 2-propanol (90:10) with a flow of 0.8 mL min^{-1}. The optical purities of **1a**, **1c** and **2c** were determined by chiral GC with a Shimadzu Gas Chromatograph GC-17A fitted with a β-cyclodextrin column (CP-Chirasil-Dex CB 25 m × 0.25 mm). A Shimadzu Auto-injector AOC-20i and FID detector were employed, and He with a linear gas velocity of 75 cm s^{-1} was used as the carrier gas. The Avantium "Quick Catalyst Screening 96" platform was used to perform the reactions in the first and second experimental designs. This equipment has a maximum pressure limit of 20 bar and the temperature is controlled for all reactors simultaneously. Otherwise, a 100 mL Parr autoclave was used. The elemental analysis was performed on a Elementar Vario EL III analyser. Commercially available NemrodW 2000 software from LPRAI (France) was used for the statistical calculations of the experimental design.

General Procedure A – Screening on the Avantium "Quick Catalyst Screening 96" Platform: The various supported metal catalysts (5 mg) were weighed into the autoclaves and added to a 1.7 M solution of the substrate in the desired solvent (1.5 mL). When water was used as an additive, 10 μL was added. In the cases in which ammonia was used as additive, the concentration of ammonia in the reaction mixture was 0.5 M. After the reaction mixture had been stirred at 90/120 °C and 20 bar H_2 for 3 or 24 hours, it was centrifuged and the supernatant liquid was analysed by GC and GC-MS.

General Procedure B – Screening for Temperature and Pressure in the Parr Autoclave: Preactivated Ni on alumina (50%, 100 mg) was added to a solution of **1a** or **1c** (5.7 mmol) in dioxane (30 mL). In the case of **1c**, water (0.2 mL) was also added. After the reaction mixture had been stirred at 80, 100, 120, 140, or 160 °C and 5, 10, 20, 30 or 40 bar H_2 for 2 hours it was filtered and the filtrate was analysed by GC.

General Procedure C – Reductions in the Parr Autoclave under Optimized Conditions for Substrates Prepared from Aromatic Aldehydes: Activated Ni on alumina (50%, 100 mg) was added to a solution of the substrate (5.7 mmol) in dioxane (30 mL). After the reaction mixture had been stirred at 120 °C and 20 bar H_2 for 3 h it was filtered, a sample (2 mL) was taken from the filtrate, and the solvents from this sample were removed under vacuum. The sample was then analysed by ^{1}H NMR spectroscopy. The combined filtrate and NMR sample were then evaporated to dryness to yield the oil or solid products.

***N*-(2-Hydroxy-2-phenylethyl)acetamide (2a):** The solid prepared from **1a** as described in General Procedure C was purified by column chromatography (silica, EtOAc/MeOH, 95:5, R_f = 0.27). Yield of **(*S*)-2a**: 503 mg (49%) as a white solid; m.p. 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.01 (s, 3 H, CH_3–C=O), 3.32 (ddd, J = 5.0, 7.9, 14.1 Hz, 1 H, CH_2–N), 3.70 (ddd, J = 3.3, 7.0, 14.1, 1 H, CH_2–N), 4.85 (dd, J = 3.3, 7.9, 14.1 Hz, 1 H, CH–O), 5.92 (s, 1 H, NH), 7.28–7.38 (m, 5 H, aromatic) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.1 (*C*H_3), 47.6 (*C*H_2–N), 73.6 (*C*H–O), 125.8, 128.8, 128.5 and 141.8 (aromatic), 171.6 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 3080, 1648, 1547, 1295 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 179 (1) $[M]^+$, 161 (3) $[M - H_2O]^+$, 120 (14), 107 (21), 79 (31), 77 (31), 73 (100). Elemental analysis calculated (%) for $C_{10}H_{13}NO_2$ (179.22): C 67.02, H 7.31, N 7.82; found C 67.00, H 7.49, N 7.81.

(*S*)-*N*-(2-Hydroxy-2-phenylethyl)acetamide ((*S*)-2a): The solid prepared from **(*S*)-1a** (95% *ee*) as described in General Procedure C was purified by column chromatography (silica, EtOAc/MeOH, 95:5, R_f = 0.27). Yield of **(*S*)-2a**: 0.454 mg (45.4%) as a white solid; *ee* = 75%, $[\alpha]_D^{20}$ = +8.1 (c = 1.0 in MeOH); other spectroscopic data as for **2a**.

***N*-[2-Hydroxy-2-(3-methoxyphenyl)ethyl]acetamide (2b):** The solid prepared from *rac*–**1b** as described in General Procedure C was purified by column chromatography (silica, EtOAc/MeOH, 95:5, R_f = 0.25). Yield of **2b**: 0.570 mg (57%) as a white solid; m.p. 123–124 °C; ^{1}H NMR (300 MHz, CD_3OD, 25 °C, TMS): δ = 1.93 (s, 3 H, CH_3–C=O), 3.28 (dd, J = 7.9, 13.7 Hz, 1 H, CH_2–N), 3.45 (dd, J = 4.6, 13.5 Hz, 1 H, CH_2–N), 3.78 (s, 3 H, OCH_3), 4.71 (dd, J = 4.6, 7.9 Hz, 1 H, CH–O), 6.81 (ddd, J = 0.9, 2.6, 8.2 Hz, 1 H, C4–*H*), 6.95 (m, 2 H, C2–H, C6–*H*), 7.24 (apparent t, J = 7.9 Hz, 1 H, C5–*H*) ppm. ^{13}C NMR (75 MHz, CD_3OD, 25 °C, TMS): δ = 22.5 (*C*H_3–CO), 48.3 (*C*H_2–N), 55.6 (O*C*H_3), 73.5 (*C*H–O), 112.6 (*C*2), 114.1 (*C*4), 119.4 (*C*6), 130.3 (*C*5), 145.5 (*C*1), 161.2 (*C*3), 173.6 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3290, 1634, 1596, 1552, 1259, 1066 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 209 (7) $[M]^+$, 191 (3) $[M - H_2O]^+$, 150 (31), 109 (25), 73 (87), 62 (46), 45 (100). Elemental analysis calcd. (%) for $C_{11}H_{15}NO_3$ (209.24): C 63.14, H 7.23, N 6.69; found C 61.41, H 7.57, N 6.50.

General Procedure D. Reductions in the Parr Autoclave under Optimised Conditions for Substrates Prepared from Aliphatic Aldehydes: Activated Ni on alumina (50%, 100 mg) was added to a solution of the substrate (5.7 mmol) in dioxane (30 mL) and water (0.2 mL). After the reaction mixture had been stirred at 140 °C and 10 bar H_2 for 2 h it was filtered, a sample (2 mL) was taken from the filtrate, the solvents from this sample were removed under vacuum, and the sample was then analysed by ^{1}H NMR spectroscopy. The combined filtrate and NMR sample were then evaporated to dryness to yield the oil or solid products.

***N*-(2-Hydroxyheptyl)acetamide (2c):** The oil prepared from **1c** as described in General Procedure D was purified by recrystallisation from EtOAc. Yield of **2c**: 454 mg (56%) as a white solid; m.p. 75–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.89 (m, 3 H, CH_3–CH_2), 1.29–1.47 (m, 8 H, CH_3–CH_2–CH_2–CH_2–CH_2), 2.00 (s, 3 H, CH_3–C=O), 3.08 (ddd, J = 5.0, 7.9, 13.7 Hz, 1 H, CH_2–N), 3.45 (ddd, J = 2.9, 6.6, 13.9 Hz, 1 H, CH_2–N), 3.45 (s, 1 H, OH), 3.69 (m, 1 H, CH–O), 6.49 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.0 (*C*H_3–CH_2), 22.6 (CH_3–*C*H_2), 23.2 (*C*H_3–CO), 25.2 (CH_3–CH_2–*C*H_2), 31.8 (*C*H_2–CH_2–CH), 35.0 (*C*H_2–CH), 45.9 (*C*H_2–N), 71.2 (*C*H–O), 171.4 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3279, 1661, 1627, 1586, 1569, 1136 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 174 (3) $[M + 1]^+$, 102 (10), 73 (100). Elemental analysis calcd. (%) for $C_9H_{19}NO_2$ (173.25): C 62.39, H 11.05, N 8.08; found C 62.01, H 11.67, N 8.04.

(*S*)-*N*-(2-Hydroxyheptyl)acetamide ((*S*)-2c): The oil prepared from **(*S*)-1c** (5.4 mmol, 94% *ee*) as described in General Procedure D was purified by recrystallisation from EtOAc. Yield of **(*S*)-2c**: 533 mg (57%) as a white solid; *ee* = 95%; m.p. 75–76 °C; $[\alpha]_D^{20}$ = +14.1 (*c* = 1.0 in MeOH); other spectroscopic data as for **2c**.

***N*-(2-Hydroxy-3-phenoxypropyl)acetamide (2d):** The oil prepared from *rac*-**1d** as described in General Procedure D was purified by column chromatography (silica, EtOAc/MeOH, 95:5, R_f = 0.29). Yield of **2d**: 967 mg (72%) as a white solid; m.p. 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.99 (s, 3 H, C*H*$_3$–C=O), 3.36 (ddd, *J* = 5.5, 6.8, 6.8 Hz, 1 H, C*H*$_2$–N), 3.59 (ddd, *J* = 3.3, 6.1, 14.0 Hz, 1 H, C*H*$_2$–N), 3.92 (d, *J* = 5.5 Hz, 2 H, C*H*$_2$–O), 4.09 (m, 1 H, C*H*–O), 4.18 (s, 1 H, O*H*), 6.58 (s, 1 H, N*H*), 6.87 (m, 2 H, aromatic), 6.95 (m, 1 H, aromatic), 7.26 (m, 2 H, aromatic) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.0 (*C*H$_3$–C=O), 43.0 (*C*H$_2$–N), 69.5 (*C*H–OH and *C*H$_2$–O), 114.5, 121.2, 129.6, and 158.4 (aromatic), 171.9 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3384, 3299, 1630, 1601, 1571, 1284, 1118, 751 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 209 (3) $[M]^+$, 191 (32) $[M - H_2O]^+$, 148 (7), 116 (100). Elemental analysis calcd. (%) for $C_{11}H_{15}NO_3$ (209.24): C 63.14, H 7.23, N 6.69; found C 61.99, H 7.22, N 6.46.

***N*-(2-Hydroxy-3-methylbutyl)benzamide (2e):** The solid prepared from *rac*-**1e** as described in General Procedure D was purified by column chromatography (silica, EtOAc/PE, 45:55, R_f = 0.30). Yield of **2e**: 681 mg (58%) as a white solid; m.p. 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.97 (dd, *J* = 6.8, 9.0 Hz, 6 H, 2 × C*H*$_3$), 1.73 (m, 1 H, C*H*–(CH$_3$)$_2$), 3.06 (s, 1 H, O*H*), 3.30 (ddd, *J* = 4.6, 8.61, 13.7 Hz, 1 H, C*H*$_2$–N), 3.50 (m, 1 H, C*H*–O), 3.72 (ddd, *J* = 2.8, 6.8, 13.7 Hz, 1 H, C*H*$_2$–N), 6.86 (s, 1 H, N*H*), 7.38 (m, 2 H, aromatic), 7.46 (m, 1 H, aromatic), 7.77 (m, 2 H, aromatic) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 17.9 (*C*H$_3$), 18.6 (*C*H$_3$), 32.3 (*C*H–(CH$_3$)$_2$), 44.1 (CH$_2$–N), 76.3 (*C*H–O), 127.0, 128.5, 131.5, and 134.3 (aromatic), 168.5 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3398, 3319, 1633, 1578, 1541, 1057, 697 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 207 (1) $[M]^+$, 189 (3) $[M - H_2O]^+$, 164 (16), 134 (89), 122 (29), 105 (100). Elemental analysis calcd. (%) for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found C 68.75, H 8.61, N 6.68.

***N*-(2-Hydroxyhepyl)butanamide (2f):** The oil prepared from *rac*-**1f** as described in General Procedure D was purified by recrystallisation from EtOAc. Yield of **2f**: 345 mg (30%) as a white solid; m.p. 62–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.89 (m, 3 H, pentyl-C*H*$_3$), 0.95 (t, *J* = 7.5 Hz, 3 H, propyl-C*H*$_3$), 1.29–1.44 (m, 8 H, CH$_3$–C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_2$), 1.67 (sext, *J* = 7.4 Hz, 2 H, C*H*$_2$–CH$_2$–C=O), 2.18 (t, *J* = 7.4 Hz CH$_2$–C*H*$_2$–C=O), 2.94 (s, 1 H, O*H*), 3.11 (ddd, *J* = 4.9, 7.7, 13.0 Hz, 1 H, C*H*$_2$–N), 3.47 (ddd, *J* = 2.7, 6.2, 13.7 Hz, 1 H, C*H*$_2$–N), 3.70 (m, 1 H, C*H*–O), 6.15 (s, 1 H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.8 (propyl-*C*H$_3$), 14.0 (pentyl-*C*H$_3$), 19.2 (*C*H$_2$–CH$_2$–C=O), 22.6 (CH$_3$–*C*H$_2$–CH$_2$–CH$_2$), 25.2 (CH$_3$–CH$_2$–*C*H$_2$–CH$_2$), 31.8 (*C*H$_2$–CH$_2$–CH), 35.0 (*C*H$_2$–CH), 38.6 (*C*H$_2$–C=O), 45.7 (*C*H$_2$–N), 71.5 (*C*H–O), 174.2 (*C*=O) ppm. IR (KBr): $\tilde{\nu}$ = 3418, 3283, 2964, 2919, 1657, 1624, 1566 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 130 (17), 101 (100), the $[M]^+$ peak could not be identified. Elemental analysis calcd. (%) for $C_{11}H_{23}NO_2$ (173.25): C 65.63, H 11.52, N 6.96; found C 64.78, H 12.03, N 6.83.

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