Organic Process Research & Development 2008, *12,* 512–521

Optimization and Scale-up of a Pd-Catalyzed Aromatic C−N Bond Formation: A Key Step in the Synthesis of a Novel 5-HT_{1B} Receptor Antagonist

Hans-Jürgen Federsel,*,† Martin Hedberg,*,‡ Fredrik R. Qvarnström,‡ and Wei Tian‡

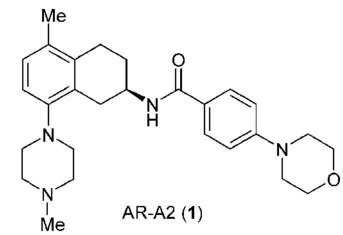
Global Process R&D and Process Chemistry, Process R&D Södertälje, AstraZeneca, 151 85 Södertälje, Sweden

Abstract:

Searching for the best synthetic route for a given target molecule is a complex task and, by the same token, a key deliverable from a process R&D department. In this vein the challenge for our group was to identify a sustainable manufacturing process for a chiral compound, AR-A2, to be developed for the treatment of certain neurological disorders. Besides designing a method for assembling the core (*R*)-2-aminotetralin nucleus, a key feature in the overall synthesis was to provide a robust procedure for creating a new C−N bond between an aromatic ring and a heterocyclic moiety. The methodology employed a Buchwald−Hartwig coupling, and a highly efficient catalytic process was developed using $Pd(OAc)_2$ as precatalyst, with loadings as low as 0.47 mol % (in laboratory trials one order of magnitude lower) together with (*R*)-BINAP as ligand. Optimizing the reaction conditions allowed a virtually quantitative conversion of the brominated aromatic substrate after heating to 110−115 °C in toluene for 4 h. Telescoping this step with a succeeding catalytic hydrogenation to effect an *N*-debenzylation, followed by precipitation of the benzoate salt offered an overall yield for the two consecutive steps of 88% at 125-kg batch size, combined with excellent stereochemical product purity of 98% ee.

Introduction

Construction of complex molecules requires an arsenal of methods and procedures. Depending on the purpose of the work, the quality of the transformations applied will have to meet varying standards. Thus, whilst small-scale bench chemistry in the laboratory should aim at being intrinsically safe and reliable, the mere fact that the amounts of material handled—intermediates, building blocks, reagents, etc.—are limited (typically <5−50 g) reduces the stringency in outcome and the performance requirements needed. However, as soon as scale-up is envisaged, the circumstances change dramatically. When aiming at producing multikilogram quantities, the chemistry has to be understood to a much higher degree in order to capture potential risks in the form of exotherms and runaway events. Moreover, it is essential to optimize yields and process throughput so that the cost of goods for the active pharmaceutical ingredient (API), a highly significant parameter, can reach acceptable levels.[1] In this case study,[2] the prime focus is development of the crucial coupling step between an aromatic moiety and a nitrogen-containing reactant to enable a commercially viable manufacturing route for AR-A2 (**1**).



AR-A2 (**1**)

This is a chiral drug that was being developed by AstraZeneca to treat an array of illnesses in the central nervous system (CNS), such as anxiety and depression. Unfortunately, during phase II clinical studies the decision was taken to discontinue further studies of this novel drug, notably due to lack of efficacy. The Buchwald−Hartwig procedure to create a new C−N bond in a catalytic mode has undergone a tremendous improvement in efficiency and output and reached a level of sophistication that looked promising for future commercial production. Failing to deliver a new drug to the market should, however, in no way blur the achievement that has been made to turn what at the time was seen as a promising academic synthetic protocol with interesting scope to carry out a wide variety of aromatic substitutions into a proven and viable methodology for large-scale production.

From Flask to Reactor: Reaching the Best Overall Route. It is not uncommon in today's pharmaceutical industry to rely on relatively poor methods for synthesizing desired compounds. The weaknesses can be exemplified as low yields, long and complex workup procedures including expensive and tedious techniques for product purification, demanding reaction conditions (pressure/temperature) which, when combined, lead to an unsustainable cost of the final product from a marketing point of view. This is the scenario often confronted in the early stages of R&D, typically around the point of candidate drug (CD) nomination, when process R&D will be expected to deliver the first batch of kg amounts to support wider toxicological investigations, besides development of a formulation feasible for early clinical testing and for use in first-time-in-man studies. In this regard the current project was no exception, and all in all three generations of synthetic routes were identified, developed, and put into practical use during its lifetime.[2] In order to provide the necessary background to the strategy used for the synthesis and to bring the crucial C−N bond-forming step into a broader context, the different approaches are briefly reviewed.

* Corresponding authors. E-mail: hans-jurgen.federsel@astrazeneca.com (HJF); martin.h.hedberg@astrazeneca.com (MH).

† Global Process R&D.

‡ Process Chemistry, Process R&D Södertälje.

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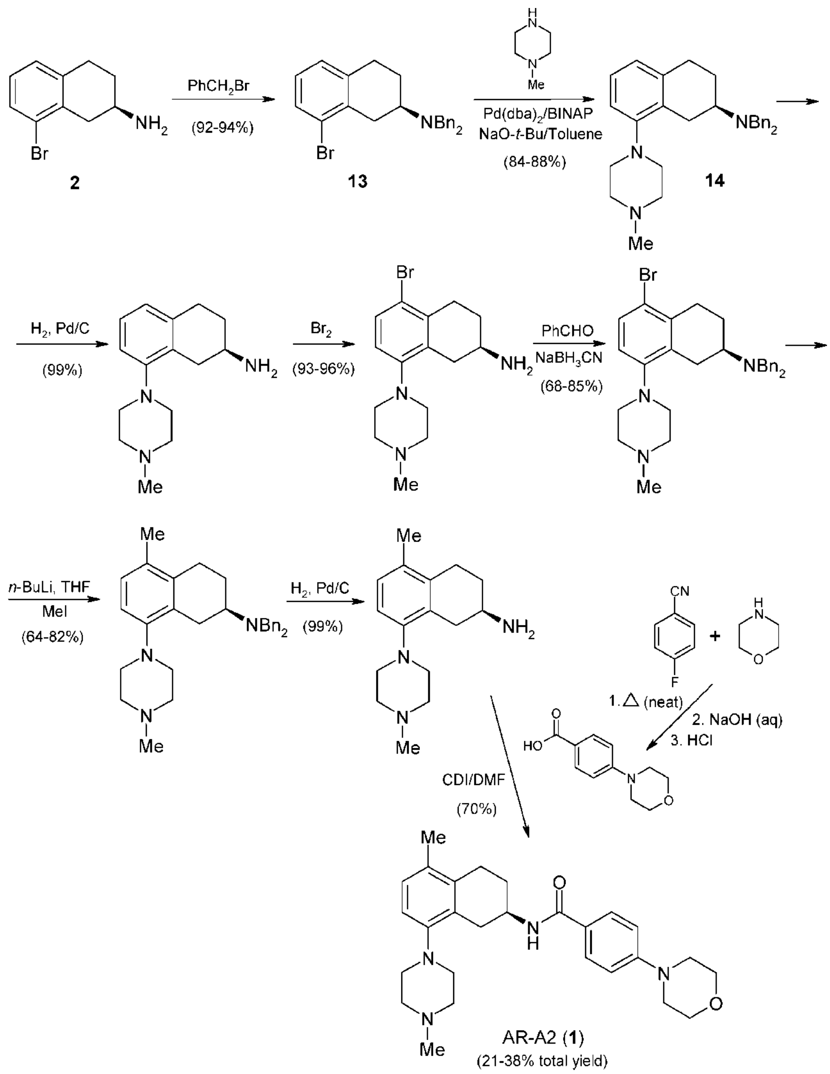
10.1021/op8000146 CCC: $40.75
Published on Web 04/26/2008

Scheme 1. **First-generation route to AR-A2 (1) applied by medicinal chemistry.**[a]



[a] Abbreviations: dba = 1,3-benzylideneacetone; CDI = 1,1′-carbonyl-di-imidazole; DMF = *N*,*N*-dimethylformamide.

Initially, the synthesis adopted by Medicinal Chemistry was seen as the best option. Their approach relied on the availability of chiral aminotetralin **2** (see Scheme 1) in high stereochemical purity, which had the advantage that there was no need for a *de novo* construction of the core tetrahydronaphthalene part nor for generating the desired configuration (*R*). A major downside, however, was the limited availability and cost ($50,000−100,000/kg) of the des-methyl-tetralin starting material. This starting material required that the methyl group be introduced by using a problematic low-temperature lithiation/methylation procedure. So, in spite of a reasonable 21−38% overall yield, this route (see Scheme 1) was abandoned.

In the second-generation route, the synthesis was further back-integrated such that the tetralin moiety was created from 3-methylphenyl acetic acid (**3**). A key step in this sequence was the formation of tetralone **5** from precursor **4a**[3] using ethene as an ideally suited C_2-building block under Friedel−Crafts-like conditions.[4] This transformation proceeded surprisingly well, and yields of 60−70% were generally obtained. The main bottleneck in this considerably more scale-up friendly synthetic route was the reductive amination of ketone **5** [using NaBH(OAc)$_3$][5] followed by a one-pot resolution with unnatural tartaric acid leading to **6** (see Scheme 2). Even after investing a large resource the total yield in this two-step process could not be increased above 25% which, eventually, disqualified this option for further development.

Nonetheless, inspired by the improvements seen when running the manufacture on pilot-plant scale, it was felt that the basic route was correct. The intrinsic weakness was the resolution, and this eventually led to the use of (*S*)-1-phenylethylamine (**8**) to induce asymmetry in the tetralin. This approach has been shown to work when performing the imine reduction under appropriate conditions.[6] Thus,when applying a two-stage procedure consisting of imine formation using **8** as chiral handle, followed by reduction ($NaBH_4$ in MeOH/*i*-PrOH), resulted in a 4:1 mixture of substituted tetralin **9** in favour of the desired (*R*,*S*) diastereomer. Interestingly, carrying

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(4) (a) Sims, J. J.; Selman, L. H.; Cadogan, M. *Org. Synth.* **1971**, *51*, 109–112. (b) Hunden, D. C. *Org. Prep. Proced. Int.* **1984**, *16* (3−4), 294–297.
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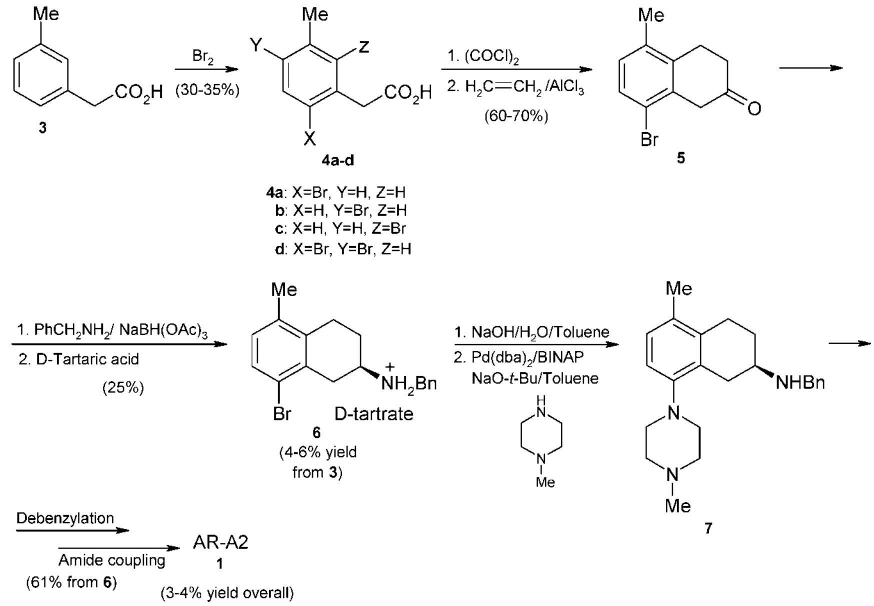
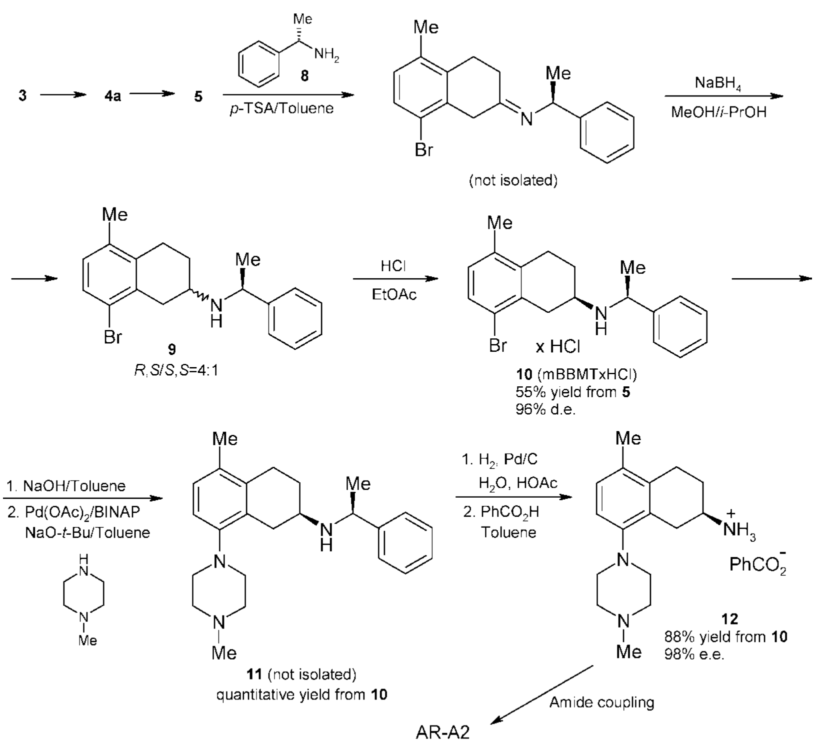
(6) Kanai, Y.; Saitou, K.; Koki, U. Japan Kokai Koho 10,072,411, 1998.

Scheme 2. **Second-generation route to AR-A2: an improved, scale-up friendly synthesis of 1 that requires resolution of a racemic intermediate.**



Scheme 3. **Third-generation route: a diastereoselective synthesis of AR-A2 (1) using (*S*)-1-phenylethylamine (8) as a crucial, multi-tasking component.**



it out as a one-pot reaction led to a 3:2 (*R*,*S*)/(*S*,*S*) diastereomer composition. Formation of an HCl salt followed by a simple polishing crystallization gave intermediate **10** with 96% de in a 55% yield from tetralone **5**. Running the reaction under a slightly different experimental protocol ($NaBH_3CN$) and solvent system (MeOH/THF, 1:1) failed to give any asymmetric induction at C-2.[7] The chiral induction offered by (*S*)-phenylethylamine proved to be successful enough so that no resolution would become necessary, which for obvious reasons was seen as a decisive step-change in reaching better process efficiency. This sequence, which also became the last one to be developed and operated on pilot scale before closing the project, is shown in Scheme 3.

Common to all routes described above was the need for conducting a suitable coupling between the aromatic nucleus of related but varying tetralin species and a defined piperazine side chain somewhere along the synthetic sequence. The protocol that was immediately identified as being capable of

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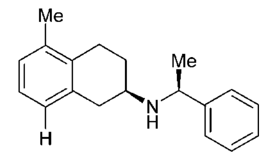
responding to this task and generating the required C−N bond was the Buchwald−Hartwig procedure. From its invention in the late 1990s it has been demonstrated to perform with a wide variety of substrates and reactants;[8,9] however, reports of scale-up and bulk production are still scarce. The specific application of this chemical transformation on our case and the tremendous development that the method has undergone, together with experience from upscaling gathered over the course of the project life cycle, are herewith disseminated and explored in detail.

Mastering C−N Bond Formation: Development and Optimization. In order to put the versatility of this aromatic substitution reaction and its relative user-friendliness into a broader context, suffice it to say that in a very early and premature version of our synthetic effort to create Ar-piperidino motifs, other well-documented standard procedures were applied. Thus, one approach starting from a phenol precursor made use of the Smiles rearrangement[10] as a key reaction step, a methodology emanating from the 1930s requiring stongly basic conditions (NaH) and elevated temperatures (130 °C). This created an anilino-derivative that could be transformed to the piperazine-substituted product using a suitable reactant under reductive conditions. In the other route, the heterocycle was again constructed from an aniline by conducting a double alkylation using an *N*,*N*-*bis*-2-chloroethylamine as building block, a renowned carcinogen with pronounced toxic properties.[11–13] These protocols were deemed unsuitable for large-scale production by virtue of the many steps and hazardous chemistry involved.

The need for alternative approaches is, thus, easily emphasized, and as it turned out, help was not too far away in the form of a homogeneous, metal-catalyzed procedure pioneered independently by Buchwald[14] and Hartwig,[15] respectively. Attractive features of this route were the catalytic protocol allowing low catalyst loading, and the high yields that had been reported by the inventors. A further benefit was the conciseness of the methodology that enabled abundantly available aromatic chlorides or bromides to be directly coupled with the appropriate amine moiety in just one step, totally avoiding the multistage procedures described above. Hence, with this seemingly powerful tool at our disposal we focused all our attention to this novel reaction type.

Starting with the first-generation synthesis of the target molecule AR-A2, **1** (see Scheme 1) the Buchwald−Hartwig reaction had already been successfully applied with 84−88% yields in large laboratory-scale runs. Using $Pd(dba)_2$ as the precatalyst, initially at 3.1 mol %, but later demonstrating that this could be more than halved (to 1.5 mol %) at 200-g scale, with (*R*)-BINAP as ligand in the presence of NaO-*t*-Bu in toluene, a method was developed that provided a straightforward access to the desired piperazinyl-substituted tetralin motif.

When proceeding to the next synthetic sequence for **1**, the overall procedure for making the final product was considerably improved as there were fewer steps and better prospects for successful scale-up. In this case the coupling reaction with the piperazine moiety was conducted on a mono-(**6**) rather than dibenzyl-amino structure (**13**). An obvious risk was the competing intermolecular dimerization using a secondary amine. Much to our surprise, no formation of this dimer could be detected, and the yield of compound **7** remained >80%. The only noticeable byproduct formed was the 8-*H* derivative **15**, albeit in sufficiently small amounts (<2%) not to cause any problems downstream.



15 (8-*H* analogue)

Closer examination of the reaction rate provided the opportunity to reduce the catalyst loading from 1.5 mol %. Indeed, the chemistry was found to work at a catalyst loading as low as 0.1 mol %, but reaction time increased from 4 to 20 h. A process compromise was reached at 0.4 mol % catalyst added in 2 portions. Encouraged by these findings, this step was scaled up for pilot plant production where in total about 30 kg of the (*R*)-8-piperazinyl-*N*-benzyl-2-aminotetralin **7**was obtained in excellent quality. This was ultimately converted to one batch of 26 kg of **1**.

Operating in a partially asymmetric fashion the third and final route has the potential to provide the most efficient process, and accordingly, a programme was devised to test for good process understanding and to conduct optimization work along the entire sequence. Focussing specifically on the Buchwald−Hartwig step, the feeling was that the previous studies had developed the method to a relatively advanced level, especially considering the first pilot run. Unfortunately it turned out to be the opposite, as the established experimental conditions on free base substrate **10** (Scheme 3) gave disappointing results in the initial pilot trials showing a pronounced increase in the 8-*H* analogue **15**. Widely differing results gave a lack of robustness—in the worst case up to as much as 11% impurity 8-*H* (**15**) on 23-kg scale in 600 L reactor size. Another problem observed was the precipitation of the Pd catalyst from the reaction mixture in the form of a solid, brownish material. The existing protocol was obviously insufficiently robust to accommodate a new substrate (**10**), irrespective of the close resemblance to the structure of compound (**6**) that it had originally been developed for. Thus, a thorough investigation into the reasons and mechanisms behind the formation of the undesired *H*-analogue **15** was launched.

Based on on literature precedence,[16] it was thought that the amine reactant (1-methylpiperazine) was the hydride donor by

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Table 1. Key experiments for the Buchwald−Hartwig coupling

entry	altered conditions[a]	product **11** after 3 h(% GC)	8-*H* analogue **15** after 3 h(% GC)	remarks
1	*rac*-BINAP as ligand	99	0.3	
2	Xantphos as ligand	62	7	
3	(o-tol)$_3$P as ligand	18	14	xylene 130 °C
4	NaOMe as base	10	6	
5	NaOEt as base	0	0	
6	xylene, 130 °C	99	0.7	<30 min to full conv.
7	0.1 equiv (= 0.06% v/v) H_2O	99	0.7	
8	under noninerted conditions	99	1.2	slight increase in **15** was stillwithin the normal variation
9	1.4 equiv BINAP to $Pd(OAc)_2$	88	11	
10	2 equiv BINAP to $Pd(OAc)_2$	96	3.1	
11	5 equiv BINAP to $Pd(OAc)_2$	99	0.3	

[a] Normal conditions are 1.0 equiv of **10** free base, 2.0 equiv of *N*-methylpiperazine, 0.0047 equiv of $Pd(OAc)_2$, 0.02 equiv of (*R*)-BINAP, 1.4 equiv of NaO-*t*-Bu, in toluene at 110−115 °C for 4 h and operating under an inert atmosphere of N_2. Thus, the crucial BINAP/$Pd(OAc)_2$-ratio is set at 4.25:1. Listed in the table are deviations from this experimental protocol.

virtue of a β-elimination mechanism. This hypothesis was found not to be entirely correct, as excluding the piperazine moiety from the reaction mixture still produced **15** (29% after 30 h reaction time; two other impurities were generated alongside in a total amount of about 5%, but these were not pursued further). Our conclusion was that other hydride sources were involved, foremostly the α-methylbenzylamine moiety, which by virtue of its secondary acyclic amine structure with α-branching shows much higher propensity for hydride donation.[17] Furthermore, the base (NaO-*t*-Bu) might exert an influence and contribute to this side reaction. The problem of uncontrolled formation of **15** was systematically approached by scanning a range of potential factors: both the individual constituents present in the system as well as different aspects of the reaction conditions. Broad examination covered parameters such as the H_2O content, the relative amounts of 1-methylpiperazine and *tert*-butoxide, variations in the charging order of reactants, the absolute concentration of the reaction mixture, benefits from operating under inert atmosphere, temperature, time, amount of ligand and metal and the ratio between them. From the vast amount of data generated, some parameters were linked more strongly to the formation of **15**. (a) In spite of some inconsistencies there is a clear relationship to the amount of 1-methylpiperazine, although differences are small in the range scrutinized most carefully (1.6−2.2 equiv); (b) butoxide at nearly equimolar amounts (1.1−1.2 equiv) showed a strong effect (up to 50% **15**), while in the normal operating range (1.4−1.6 equiv) the content was reduced to 0.3−14%, a trend that was further augmented when running at >2 equiv (1.5−1.9%); (c) the relationship between ligand (BINAP) and metal precatalyst (Pd-salt) has the most pronounced and unambiguous effect with a tendency that a ligand/Pd ratio <2 generated **15** as high as 10% or above, while a ratio of >2.5 guaranteed that the amount would be lowered to <1.6%. In this context, a comprehensive factorial design study was performed to gain further insight into the relation between various parameters, and to establish a quantitative basis for better process optimization. The results clearly revealed that the main factor was the ligand/Pd ratio which had to be kept >2.5 in order to minimize formation of **15**. It was also evident that the base (NaO-*t*-Bu) played some role and should, therefore, be used at a higher level (1.4 equiv) compared with the level used in the "standard" procedure (1.1 equiv). It had been established early on that switching the precatalyst from $Pd(dba)_2$ to $Pd(OAc)_2$ was beneficial,[18] not only as a consequence of a lower cost per mole but also from the point of view of reaction performance. Finding the optimal ligand, however, was still an issue of highest priority and the initial choice of (*R*)-BINAP had largely been steered by what was reported in the literature at the time. This was now challenged in a search for competitive alternatives. The main focus of our screening studies and evaluation became (1) the cost of the ligand hoping that it might be less than BINAP; (2) the temperature for conducting the reaction, where the aspiration was to operate at a lower level than before (110−115 °C). In connection with this we also evaluated the base, by comparing the results achieved when using various alkoxides and carbonates, as well as the influence of water and solvent type. The outcome of these investigations are summarized in Table 1, from which the following conclusions can be drawn: (i) BINAP constitutes the best ligand (entries 2 and 3); (ii) racemic versus enantiopure BINAP is of no importance (entries 1 and 11); (iii) the choice of base is crucial (entries 4 and 5); (iv) the reaction tolerates up to 0.06% v/v H_2O (entry 7); (v) changing of solvent from toluene to xylene has only a marginal effect on the yield, but significantly accelerates the reaction rate since it allows the reaction to be performed at higher temperatures (entry 6); (vi) shifting from inert to noninert atmosphere during the reaction has an almost negligible effect (entry 8). It is worth mentioning that besides the ligands reported in Table 1, representing both the mono- and bidentate classes, we also evaluated some other alternatives belonging to the former group. Of those tested, tri-*tert*-butylphosphine stood out as the best, albeit with a slow reaction rate and a ratio between product and *H*-analogue of 6:1, which was felt to be not good enough to be taken forward. Furthermore, from a performance aspect, it was found that the only base competitive with sodium *tert*-butoxide, was the homologous sodium *tert*-pentoxide. The latter has the advantage

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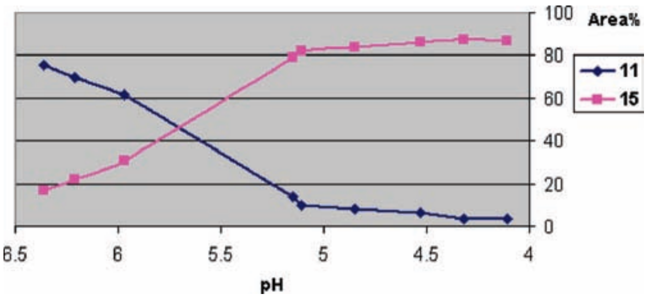

Figure 1. **Area % of 11 and 15, respectively, in the toluene phase as a function of pH in the H_2O phase used in the extraction.**

of being considerably more soluble in the preferred solvent toluene, in which the rate of reaction remained roughly constant, albeit that the *H*-analogue **15** was formed to a somewhat larger extent. As there was no cost benefit using pentoxide, this option was not pursued.

Designing the Final Process. Having optimized the catalyst loading in the Buchwald−Hartwig reaction to ensure a quantitative conversion of starting material resulting in high productivity, design of an effective workup and isolation remained. The key development target was to reduce or eliminate the amount of the 8-*H* analogue **15**, normally 1.8−6% using the optimized protocol, as early in the workup as possible to ensure that it would not be carried along further downstream. The reason was that if the purification was postponed to the final stage, previous work had shown separation of the 8-*H* congener from the final product AR-A2 was inefficient and would cause a loss of valuable product. This approach was, therefore, suspended as not sustainable for reaching the specification limit of <0.5% byproduct. Instead it was felt that utilizing the difference in product and impurity pK_a by careful adjustment of the pH should be successful. The impurity (**15**) has pK_a 9.29, and the product (**11**) with three basic nitrogens has pK_as of 9.48, 8.89, and 3.05. Evaluating a wide pH range from 4 to 13 showed good separation with a maximum of 83 area % (GC) of **15** in the toluene phase at pH 5, whilst **11** was at a level of only 8 area %. Fine-tuning revealed that the optimum pH value was between 5.1−5.3, where the carry-over of **15** into the H_2O phase would be minimized, at the same time achieving a minimal loss of **11** in the organic layer. The pH dependence of compounds **11** and **15**expressed as their relative presence in the toluene phase is shown in Figure 1. Switching from the previous method where the extraction was carried out at pH ≤ 2 and instead operating around pH 5, gave a purer process stream for further work-up and, moreover, an efficient separation of **15** at minimum loss of **11**. Furthermore, this change enabled the process to be carried out in standard stainless steel reactors, lessening the risk of reactor corrosion. Summarizing the experimental studies, optimizations, and pilot runs into a fine-tuned process description, the C−N bond-forming Buchwald−Hartwig step was designed as described in the flowchart in Figure 2. It had become clear that the best way to ensure a successful transformation from **10** free base to **11** was to conduct a premixing operation of $Pd(OAc)_2$, BINAP, and methylpiperazine in toluene while heating the mixture to 45 °C before charging to the substrate (after liberating the free base) in the main reaction vessel. This procedure guaranteed the formation of an active catalytic complex that was found, fortuitously, to be very stable and, hence, user-friendly, as demonstrated by its tolerance towards water and normal atmospheric conditions. In spite of laboratory evidence showing that the reaction could be performed in a validated manner at a catalyst loading as low as 0.065 mol % Pd and yet obtain full conversion after 2 h, it was decided for practical reasons to stay with the already established level of 0.47 mol % with the main reason being the increased risk of facing a charging error in case the catalyst amount was taken too far down; running on a 100 kg batch size under such conditions the total amount of $Pd(OAc)_2$ to be added to a 2000 L reactor would be merely 38 g, and it was felt that full repeatability of this operation would be difficult to achieve. After a 4-h reaction time in refluxing toluene, the process stream was submitted to an extractive workup as described above before directly taking the product-rich H_2O phase to the next stage. Here a “classical” catalytic debenzylation was conducted with the help of Pd on charcoal and H_2, before precipitating the desired product as the benzoate salt **12** in 88% overall yield from **10** and in stereochemical purity of 98% ee.[2] Another important quality aspect relevant to patient safety, is the amount of residual heavy metal remaining in the isolated product. This concern is especially pronounced when conducting organometallic reactions, such as the Buchwald−Hartwig,[19] in homogeneous phase, and reaching the low ppm levels requested by the authorities can often be quite challenging. Fortunately, in our case virtually all Pd disappears in the toluene stream after the acidic extractive workup at pH 4−6 (flowchart in Figure 2), leading to the final intermediate **12** showing a Pd content below the regulatory acceptance limit for APIs.

Conclusions

In this contribution, which represents excerpts from a major drug project undertaken in our Process R&D organization from the late 1990s into 2000, we have focused on one crucial step in the synthetic sequence: the formation of a C−N bond between an aromatic moiety and a heterocyclic building block. During the course of the development, three different routes for making the target molecule AR-A2 (**1**) were designed and evaluated; in each, creation of the C−N bond was a key component. The Buchwald−Hartwig coupling procedure enables synthesis of the C−N bond in a catalytic manner using $Pd(OAc)_2$ and (±)-BINAP. We have developed, refined, and optimized the protocol tailored to our specific bromo-aminotetralin and *N*-methylpiperazine. The final process (Scheme 3; flowchart in Figure 2) operates at a high capacity with only about 0.5 mol % Pd and produces the desired product (**12**) in a telescoped fashion, where the coupling is combined with a catalytic hydrogenation to effect a debenzylation. Overall performance has been validated in the pilot plant, where batches

(19) An approach to the Buchwald−Harttwig amination making use of the catalyst in heterogenous form on a fibre-support has recently been published. Christensen, H.; Kiil, S.; Dam-Johansen, K.; Nielsen, O. *Org. Process Res. Dev.* **2007**, *11* (6), 956–965.

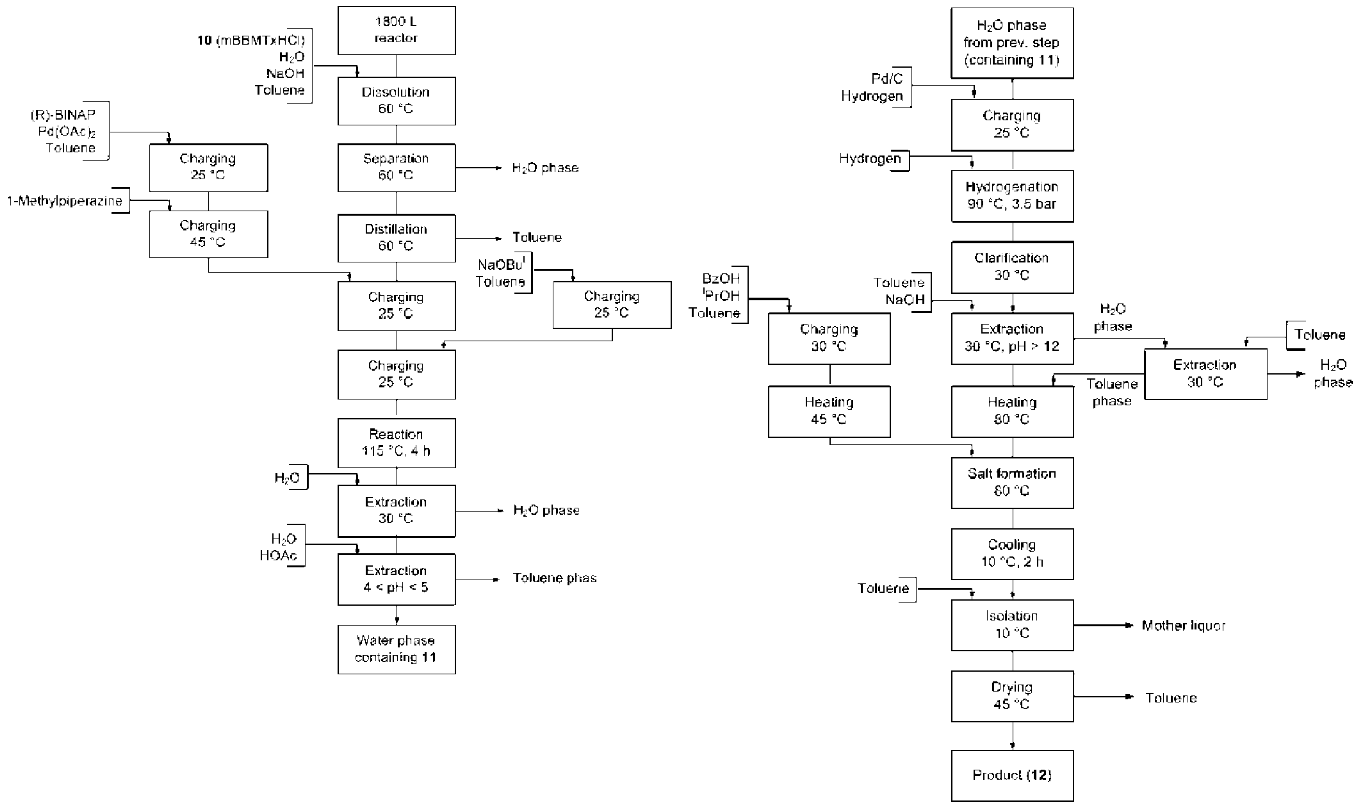

Figure 2. **Fully integrated process of converting the bromo-aromatic intermediate 10 (mBBMT×HCl) to the piperazine-substituted product 12 in two stages; a homogenous Pd/BINAP-catalyzed Buchwald−Hartwig coupling followed by a heterogeneous catalytic hydrogenation effecting debenzylation.**

of 125 kg material (88% yield over two stages) has been manufactured at an impeccable quality (98% ee).

Experimental Section

General. NMR spectra were taken on a Bruker 400 Ultra Shield instrument operating at 400 MHz, and chemical shifts are reported in parts per million (ppm) with the respective deuterated solvent peak as an internal standard. HRMS data were recorded using ESI positive or negative ionization mode depending on the compound. Reagents and solvents were obtained from commercial sources and used without further purification. Optical rotation measurements were performed using an Optical Activity AA-5 automatic polarimeter, a 200 mm cell, and the sodium D-line as wavelength at room temperature.

2-Bromo-5-methylphenylacetic Acid (4a).[3] K_2CO_3 (257 kg, 1.86 kmol) and H_2O (999 L) were mixed under nitrogen in a 2500 L glass-lined reactor. 3-Methylphenylacetic acid (**3**) (300 kg, 2.00 kmol) was added, and the resulting mixture was agitated with release of carbon dioxide, giving a solution of the potassium salt of **3**, which was cooled to 10 °C. Br_2 (l) (325.8 kg, 2.05 kmol) was charged over 3 h via a dip pipe under vigorous agitation, maintaining the temperature <15 °C. During the bromine addition more carbon dioxide was released. After the addition was complete, the resulting solution was stirred for 1 h at 10 °C. Excess bromine was destroyed by adding sodium sulfite (3.0 kg), and the resulting mixture was allowed to reach 15 °C. The solution obtained was then added over 1.5 h to another 2500 L glass-lined reactor containing a mixture of H_2O (400 L) and 33% HCl (aq) (196 L, 2.06 kmol) at 15 °C. The first reactor and the associated tubings were rinsed with H_2O (50 L), and this aqueous portion was added to the main mixture. The resulting suspension was stirred for 1.5 h at 15 °C before the solids were isolated by centrifugation. The three centrifuged portions were rinsed with 200 L of H_2O each, which gave 570 kg of crude solid material as a wet cake, containing 20% w/w of H_2O, and the isomer distribution was 55/34/8 for isomers **4a**/**4b**/**4c**, respectively, according to HPLC. This crude product also contained about 1% of dibrominated analogue **4d**. This material was purified by crystallization as described below.

The crude product prepared as described above (958 kg) was dissolved in a mixture of H_2O (892 L), *i*-PrOH (843 L) and HOAc (153 L) in a 3000 L glass-lined reactor at 60 °C. The obtained solution was cooled to 0 °C over 6 h, during which, first, an emulsion was formed, followed by a white suspension. After stirring at 0 °C for 2.5 h, the solids were isolated by centrifugation. This gave 384 kg of a wet product consisting of a mixture of **4a**, **4b**, and **4c** with a regioisomer distribution of 80/14/4, respectively, according to HPLC and a loss on drying of 15%. This material was dissolved in a mixture of H_2O (576 L) and *i*-PrOH (334 L) at 60 °C, after which the resulting solution was cooled to 0 °C over 4 h. During this time a white solid precipitated, generating a suspension, which was agitated at 0 °C for another 2 h. The solid was isolated by centrifugation in two portions, and each portion was rinsed with H_2O (200 L). Drying at 60 °C and <2 kPa gave 247 kg (32%

assay-corrected yield) of **4a** with 95% purity and an isomer composition of 95/2.5/1.5 for **4a/4b/4c**, respectively, according to HPLC.

Melting point 119−122 °C (uncorrected) [lit.[3] 122−123 °C]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1 H), 7.78 (d, J = 8 Hz, 1 H), 7.52 (app d, J = 2 Hz, 1 H), 7.34 (app dd, $J1$ = 2 Hz, $J2$ = 8 Hz, 1 H), 3.98 (s, 2 H), 2.57 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 137.4, 135.0, 133.1, 132.2, 129.8, 121.5, 41.3, 20.6; HRMS $C_9H_8O_2Br$ $(M - H)^+$ calcd 226.9708; found 226.9719.

8-Bromo-5-methyl-3,4-dihydro-1H-naphthalen-2-one (5).[4] Compound **4a** (204.0 kg, 891 mol) was mixed with 1,2-dichloroethane (727 L) and *N,N*-dimethylformamide (0.14 kg, 1.9 mol) in a 2500 L glass-lined reactor. The obtained mixture was heated to reflux (82 °C jacket temperature) before addition of thionyl chloride (128.2 kg, 1078 mol) over 2.5 h. After completed addition, the mixture was refluxed for another 2 h and cooled to a temperature of 58 °C; at this temperature a sample showed complete conversion to the acid chloride. This mixture was cooled to 26 °C and was then concentrated by vacuum distillation at 26−33 °C and 9.5−10.2 kPa until approximately 612 kg of volatiles had been removed. 1,2-Dichloroethane (500 L) was added to the residue, and the resulting solution was cooled to −2 °C before addition of $AlCl_3$ (133.0 kg, 997.5 mol) over 0.5 h under efficient stirring, while keeping the temperature between −4 to +2 °C. A further portion of 1,2-dichloroethane (55 L) was used to rinse the reactor walls from solid $AlCl_3$, and this portion was pooled with the main suspension. Ethene (g) (60.6 kg, 2.16 kmol) was added through a dip pipe over 6 h 20 min, which gave a steady inner temperature of between −1 to +1 °C for this strongly exothermic reaction. The mixture was stirred at 0 °C for an additional 30 min, before analysis showed complete conversion. Transfer of the mixture to a second 2500 L glass-lined reactor containing H_2O (710 L) was performed over 4 h at temperatures between 10−24 °C. The first vessel and the connected tubings were rinsed with 1,2-dichloroethane (50 L) and this portion was added to the two-phase system thus obtained, which was heated to 25 °C and stirred at this temperature for 30 min before agitation was stopped and the phases were allowed to separate. The organic layer still contained some aqueous residues, and it was therefore heated to 28 °C and left for another 45 min before conducting the second phase separation. $KHCO_3$ (85.0 kg) and H_2O (760 L) were added to a second 2500 L glass-lined reactor, and the resulting solution was heated to 25 °C before mixing it with the organic phase above. This two-phase mixture was stirred, maintaining the temperature at this level for 30 min, before being allowed to settle for 1 h. The organic layer was then washed with H_2O (750 L) at 28 °C before a concentration was conducted by vacuum distillation at 20−25 °C and around 10 kPa until approximately 231 kg of volatiles had been removed. This gave 1008 kg of a 14% w/w solution of crude tetralone **5** to be purified by crystallization as described below.

The solution obtained above (1008 kg) was concentrated by vacuum distillation until approximately 662 kg of volatiles had been removed. Methylcyclohexane (240 L) was added to the residue, and the resulting mixture was further concentrated by vacuum distillation until approximately 212 kg of volatiles had been removed. A second portion of methylcyclohexane (160 L) was added, and the vacuum distillation was repeated until 190 kg of volatiles had been removed. A third portion of methylcyclohexane (160 L) was added, and the vacuum distillation was repeated until 119 kg of volatiles had been removed. Subsequently, the residual amount of 1,2-dichloroethane was only 0.4% as determined by GC. Di-isopropyl ether (70.2 kg) was added to the residue at 30 °C followed by methylcyclohexane (325 L) allowing the temperature to reach 25 °C. The resulting suspension was agitated at this temperature for 0.5 h before cooling over 3 h to −5 °C. Solid material was isolated by centrifugation giving 139.3 kg of **5** (52.2% yield, corrected for assay and purity, from compound **4a**) having a loss on drying value of 7.6% w/w and a GC purity of, in this case, 86.4 area %. The purity of compound **5** has varied between 83−93% comparing eight batches on similar scale. This material was taken forward to the reductive amination step without further purification.

(*R*)-8-Bromo-5-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)-(*S*)-1-(phenylethyl)amine Hydrochloride (10). Compound **5** (170 kg, 90% purity by GC, 711 mol) was charged to a 2500 L glass-lined reactor under nitrogen atmosphere. Toluene (731 L) was added, the resulting solution was mixed with *p*-toluenesulphonic acid monohydrate (493 g, 2.59 mol), and the resulting solution was agitated at 30 °C. (*S*)-Phenylethylamine (**8**) (86.2 kg, 711 mol) was added, and the mixture obtained was concentrated by vacuum distillation at 35−50 °C and 4−30 kPa until approximately 459 kg of volatiles had been removed. At this point, a >98% conversion to the imine/enamine had been obtained. The residue was mixed with MeOH (680 L) and *i*-PrOH (901 L), and the resulting solution was cooled to −3 °C. $NaBH_4$ (50.0 kg, 1.32 kmol) was added in 5-kg portions in such a way that the inner temperature did not exceed 10 °C. After complete addition, the mixture was stirred for 7 h at 10 °C. Since the conversion was not >96% at this point, two additional portions of $NaBH_4$ (5.0 kg, 132 mol each) were added, and agitation was continued at 10 °C for another 3 h. The mixture was then heated to 35 °C for 30 min to destroy residual $NaBH_4$ (this is important to avoid foaming in the distillation described below). The resulting mixture was concentrated by vacuum distillation at 35−45 °C and 10−30 kPa until approximately 917 kg of volatiles had been removed. Toluene (690 L) and H_2O (646 L) were added to the residue, and this mixture was agitated for 1 h at 47 °C. The aqueous layer was removed, and the organic phase was concentrated by vacuum distillation at 35−55 °C and 3−25 kPa until approximately 818 kg of volatiles had been removed. EtOAc (629 L) was added to the residue, and the resulting mixture was transferred to a second 2500 L glass-lined reactor via a GAF filter. The first reactor and the filter were rinsed with EtOAc (100 L). The solution obtained was diluted with absolute EtOH (313 L) and heated to 58 °C. HCl (g) (39.1 kg, 1.07 kmol) was added via a dip pipe at 60 °C over 3 h. After complete addition, the resulting suspension was agitated at 60 °C for 2 h and then cooled to 15 °C over 1.5 h. After the solution stirred at 15 °C for 1 h and the pH of the mother liquor was checked to make sure it was <2, the white solid was isolated by centrifugation. Each of two loadings on the centrifuge was washed with EtOAc (120 L per portion) giving a total of 256 kg of wet crude **10** (HCl salt) having 94% diastereomeric excess (de), 30% loss on drying, and a chromatographic purity of 99% by GC. This material was subjected to the recystallization procedure below.

Crude **10** obtained as described above (256 kg) was charged to a 2500 L glass-lined reactor under nitrogen atmosphere. Absolute EtOH (376 L) and EtOAc (877 L) were added, and the resulting suspension was stirred at 70 °C for 4 h. Cooling to 5 °C over a period of 2 h was followed by agitation at this temperature for another 1.5 h. Centrifugation and washing with EtOAc (100 L), followed by drying of the wet solid at 50 °C and 2 kPa gave 151 kg (55.8% yield) of **10** having a purity and assay >99% and a stereochemical purity of 97% de.

Melting point 286 °C dec; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.59−7.65 (m, 2 H), 7.42−7.56 (m, 3 H), 7.26 (d, J = 8 Hz, 1 H), 6.90 (d, J = 8 Hz, 1 H), 4.74 (q, J = 7 Hz, 1 H), 3.15−3.28 (m, 2 H), 2.85−2.97 (m, 1 H), 2.68−2.80 (m, 1 H), 2.43−2.62 (m, 2 H), 2.15 (s, 3 H), 1.80−1.92 (m, 1 H), 1.77 (d, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 137.7, 137.3, 137.2, 132.4, 131.1, 130.9, 130.8, 130.6, 128.7, 123.3, 57.1, 53.8, 35.3, 26.8, 25.9, 20.4, 19.4; HRMS $C_{19}H_{23}NBr$ (M + H)$^+$ calcd 344.1014; found 344.1018; $[\alpha]^{22}_D$ = +18 (c 3.0, CH_3OH).

(*R*)-5-Methyl-8-(*N*^{4}-methyl-piperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ylamine Benzoate (12). Compound **10** (1.00 kg, 2.63 mol) was mixed with H_2O (1.60 kg) and 50% NaOH (aq) (0.60 kg, 7.5 mol) in a reactor at 25 °C. Toluene (7.50 kg) was added, and the resulting mixture was heated to 60 °C under stirring until all material had dissolved. The aqueous layer was removed, and the organic phase was concentrated by vacuum distillation using a jacket temperature <60 °C to a total volume of 2.2 L to remove residual water from the system. (*R*)-BINAP (32.7 g, 0.0525 mol) was charged to a second reactor, followed by $Pd(OAc)_2$ (2.75 g, 0.0123 mol) and toluene (2.3 kg), and this mixture was heated to 40 °C under stirring, which gave a solution. 1-Methylpiperazine (0.53 kg, 5.3 mol) was added to the catalyst mixture which caused a color change from orange to deep wine-red. The resulting mixture was transferred to the previously prepared toluene solution of compound **10** under stirring. In a second reactor, sodium *tert*-butoxide (0.35 kg, 3.7 mol) was mixed with toluene (1.3 kg), and the resulting suspension was vigorously agitated before transfer to the solution containing **10**, 1-methylpiperazine, and catalyst. The mixture obtained was then heated to 100 °C and kept there for 4 h, before GC analysis showed complete conversion. At this point, the reaction mixture was cooled to 20 °C, and H_2O (2.5 kg) was added. Agitation for 15 min at room (ambient) temperature was followed by phase separation and addition of a further portion of H_2O (4.0 kg) to the organic layer. HOAc (0.48 kg, 7.9 mol) was added to the two-phase system, which was then agitated at room temperature for 15 min. The pH of the aqueous layer at this point is about 5, and the two phases were allowed to settle for 1 h. The aqueous layer was then transferred to a hydrogenator. Pd/C (5% Pd, 57% H_2O w/w, 77 g) was added, and the reactor was purged with nitrogen and then evacuated. H_2 was added until reaching a relative pressure of 350 kPa, and the temperature was raised to 95 °C. The reaction was complete after 5 h, and the mixture was then cooled to 30 °C before removing the catalyst by filtration. Reactor and filter were rinsed with H_2O (0.48 L), and the rinsing water was then pooled with the reaction mixture. Toluene (3.5 kg) was added followed by the addition of 50% NaOH (aq) (760 g), and the obtained two-phase system was agitated at ambient temperature. The aqueous layer was separated and washed with toluene (2.7 kg), and this second toluene phase was pooled with the first one. A solution of benzoic acid (385 g, 3.15 mol) in a mixture of *i*-PrOH (130 g) and toluene (2.7 kg) was prepared and heated to 45 °C. This solution was added to the solution of the crude, free amine **12** at a temperature of 80 °C during 2 h under agitation. Subsequently, the jacket of the vessel was cooled to 10 °C over 2 h, and the slurry obtained was agitated for another 2 h, keeping the temperature constant at this level before filtration. After filtration the solid was rinsed with toluene (3.1 kg) and dried to give 760 g (76% yield) of pure compound **12** (benzoate salt).

Melting point 214−217 °C dec; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.92−8.00 (m, 2 H), 7.31−7.45 (m, 3 H), 7.02 (d, J = 8 Hz, 1 H), 6.91 (d, J = 8 Hz, 1 H), 3.36−3.49 (m, 2 H), 2.52−3.06 (m, 11 H), 2.39 (s, 3 H), 2.22−2.31 (m, 1 H), 2.18 (s, 3 H), 1.79−1.93 (m, 1 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 175.3, 150.2, 138.7, 135.3, 133.3, 131.5, 130.3, 129.5, 129.2, 128.9, 118.5, 56.4, 52.4, 45.8, 30.9, 28.4, 26.5, 19.4; HRMS $C_{16}H_{26}N_3$ (M + H)$^+$ calcd 260.2127; found 260.2119; $[\alpha]^{22}_D$ = +13 (c 3.0, CH_3OH).

((*R*)-5-Methyl-1,2,3,4-tetrahydro-naphthalen-2-yl)-(*S*)-1-(phenylethyl)amine Hydrochloride (15).[20] Compound **15** was isolated and purified as the hydrochloride salt from the reaction mixture of a worst case run, in which it was formed in 11 area % as mentioned in the main text. Thus, the reaction mixture (100 mL, toluene solution) was extracted with H_2O, and the organic layer was filtered to remove solid impurities and then dried azeotropically. The dried solution containing the desired product **11**, the *H*-analoque **15**, and unreacted starting material **10** was allowed to react with (*R*)-BINAP (199 mg, 0.321 mmol), $Pd(OAc)_2$ (57 mg, 0.252 mmol), 1-methylpiperazine (5.54 g, 55.4 mmol), and *tert*-butoxide (3.59 g, 41 mmol) at 80 °C for 2 h. On completion, the reaction mixture was treated with H_2O (25 mL), and the organic layer was extracted with a mixture of H_2O (100 mL) and HOAc (100%, 7.3 g). A pH measurement of the aqueous layer showed 4−5. The organic layer was evaporated to dryness and the residue was dissolved in EtOAc (40 mL). To the solution was added HCl in *i*-PrOH (6 M, 3 mL) to precipitate the salt. The white crystalline salt was collected by filtration and recrystallized from a mixture of *i*-PrOH (40 mL) and H_2O (7 mL) to obtain 3 g of **15** as the HCl salt and with a purity >98%.

Melting point 300 °C dec, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (broad, 1H), 10.08 (broad, 1H), 7.71−7.74 (m, 2H), 7.43

(20) The experimental procedure given is not directed at providing the most efficient way of synthesizing compound **15**. Instead, the protocol presents an attempt to improve the outcome of an authentic pilot trial, in which **15** had been generated to an extent of about 11%, by taking a sample and resubmitting this to Buchwald−Hartwig conditions in order to increase the yield of desired product **11**. As a spin-off exercise from this, **15** was able to be isolated and characterized.

(t, J = 7 Hz, 2H), 7.34−7.38 (m, 1H), 6.94−6.95 (m, 2H), 6.78−6.81 (m, 1H), 4.49−4.54 (m, 1H), 3.35−3.51 (m, 2H), 3.03 (broad, 1H), 2.85−2.91 (m, 1H), 2.40−2.50 (m, 2H), 2.17−2.30 (m, 1H), 2.14 (s, 3H), 2.03 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.5, 133.2, 133.1, 129.9, 129.6, 128.3, 128.1, 127.3, 126.7, 56.6, 52.8, 34.29, 25.8, 25.1, 21.5, 19.8; HRMS $C_{19}H_{23}N$ $(M + H)^+$ as the free base calcd 266.1009; found 266.1902; $[\alpha]^{22}_D = -11$ (c 1.0, CH_3OH).

Acknowledgment

The achievements in the entire AR-A2 project within Process R&D, of which the current case study presents a subsection, are the fruits of many co-workers' dedication, enthusiasm, and efforts. However, in the context of the particular piece of work forming the basis for this article, we need to specifically highlight a few names. Thus, we express our deep gratitude to Drs. Vern Delisser and Magnus Sjögren in Process Chemistry, Andreas Lindgren in Process Engineering and Göran Lundin in Analytical Chemistry (HRMS measurements), all residing at the Södertälje site. Furthermore, the great support provided by the team in Development Manufacture at Macclesfield led by Frank Harkness producing material on pilot scale is thankfully acknowledged.

Received for review January 23, 2008.

OP8000146