Construction of a Chiral Central Nervous System (CNS)-Active Aminotetralin Drug Compound Based on a Synthesis Strategy Using Multitasking Properties of (*S*)-1-Phenylethylamine

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ABSTRACT

This Account describes the design and development of a scalable synthesis for the drug molecule AR-A2 (**1**) starting from the discovery route originating in medicinal chemistry. Special emphasis is placed on the introduction of the correct (*R*) stereochemistry on C2, which was ultimately achieved in a diastereoselective imine-reducing step applying $NaBH_4$. After optimization, this transformation was operated on a large pilot-plant scale (2000 L), offering the desired product (**11**) in 55% yield and 96% diastereomeric excess at a 100 kg batch size. From a synthesis strategy point of view, the choice of (*S*)-1-phenylethylamine (**9**) was crucial not only for its role as a provider of the NH_2 functionality and the stereo-directing abilities but also as an excellent protecting group in the subsequent N-arylation reaction, according to the Buchwald–Hartwig protocol. As one of the very first examples in its kind, the latter step was scaled up to pilot manufacturing (125 kg in 2500 L vessel size), delivering an outstanding isolated yield of 95%. This consecutive series of chemical transformations was completed with an environmentally friendly removal of the phenethyl appendage. In addition, an elegant method to synthesize the tetralone substrate **6**, as well as a novel and robust procedure to use imidazole as a buffer for the selective formation of the mono-HBr salt of AR-A2, will be briefly described.

Introduction

There is an ongoing search for better medical treatment of diseases affecting the central nervous system (CNS). The breadth and multitude of illnesses in this area, coupled with their complexity and our still rather limited understanding of their etiology, makes this task an extremely challenging one. More specifically, relief of psychiatric disorders, including such mental defects as depression and anxiety, is seen as highly prioritized in light of shortcomings in existing therapies because of side effects and poor efficacy. Addressing this opportunity for improvement of a new candidate drug, AR-A2 (**1**) constituting a substituted chiral aminotetralin, was generated in the second half of the 1990s, displaying a pronounced antagonistic activity toward the 5-HT_{1B} receptor[1–3] (see Figure 1).

The Strategy in Medicinal Chemistry

At the outset, the chemistry-directed work on this class of compounds focused on a synthetic strategy based on the availability of certain 2-aminotetralin building blocks in high enantiomeric puirty. Thus, around 1990, tangible quantities of a small but growing family of various aminotetralins became accessible via a proprietary trans-

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Hans-Jürgen Federsel, born March 16, 1949, in Säter, Dalecarlia, Sweden, is a renowned specialist in the field of process R&D, where he has spent his entire professional career, spanning a period of 30 years. Starting off as a bench chemist in 1974 in former Astra at the major Swedish site in Södertälje (20 miles southwest of Stockholm), he has climbed the ranks, occupying positions both as line and project manager. After the merger that formed AstraZeneca, he has been the Head of Projects Management at the aforementioned location and was then appointed to the current role as Director of Science in Global Process R&D in the beginning of 2004. In connection with this, he was also given the prestigious title Senior Principal Scientist. The strong academic links have been further developed throughout the years after obtaining his Ph.D. degree in organic chemistry, specializing in heterocycles at the Royal Institute of Technology in Stockholm in 1980 under the supervision of Professor Jan Bergman, and this was recognized by awarding him an Associate Professorship at his Alma Mater 10 years later (1990). His long-lasting links to this institute has recently brought him a seat on the Board of the School of Chemical Science and Engineering. Publishing in peer-reviewed journals and books and frequent lecturing has rendered fame to his name that goes far beyond the limits of the own company, and Dr. Federsel enjoys invitations from all over the world to share learning and experience from his broad knowledge base on process R&D.

Martin H. Hedberg, born in 1966, received his Ph.D. degree from Uppsala University, Sweden, in 1995 under the supervision of Prof. Uli Hacksell and Dr. Anette M. Johansson. He has been a process chemist at former Astra and then at AstraZeneca since and currently holds a Team Manager position within AstraZeneca Process R&D. His work focuses mainly on the detailed understanding of chemical reactions and their scale-up to manufacture of both early development quantities as well as providing fully developed chemical processes for commercial-scale manufacture together with the staff.

Fredrik R. Qvarnström, born September 13, 1973, in Solna, Sweden. He studied chemistry at Stockholm University, where he obtained his M.Sc. degree in 1999. He joined AstraZeneca in 2000, where he now holds the title Senior Scientist.

Magnus P.T. Sjögren, born in 1962, studied at the Royal Institute of Technology in Stockholm, followed by a period at the University of Sydney, where he completed his Master's degree in 1987 in chemical engineering. He returned to the Royal Institute of Technology to conduct his thesis work under the supervision of Prof. B. Åkermark, studying palladium-catalyzed nucleophilic substitution of allylic leaving groups. A portion of the studies was performed at the Universita di Napoli in Italy under the supervision of Prof. A. Vitagliano. After receiving his Ph.D. degree in 1993, Dr. Sjögren started as a Process Chemist in Process R&D at former Astra in Södertälje, Sweden. Over the years, he has been involved in approx 25 drug-development projects, occupying different positions, and has been based both in the U.K. and Sweden. His current position in AstraZeneca is Associate Director in Process Chemistry, Process R&D Södertälje.

Wei Tian, born in Harbin, China, on May 1, 1958, received his M.Sc. degree from Dalian University of Technology in China in 1986. He started his overseas study at The Swedish University of Agricultural Sciences in 1989 and received his Ph.D. degree in 1993 under the supervision of Professor Kjell Olsson. After his Ph.D. degree, he joined Glycorex, a biotech company, and worked on the synthesis of oligosaccharides active for binding antigens of different types of blood. Dr. Tian joined Process R&D Södertälje of former Astra in 1997 as a Senior Scientist and was promoted to Associate Principal Scientist in 2002. His work in the last 10 years has focused on the process development of new drugs in the area of CNS diseases.

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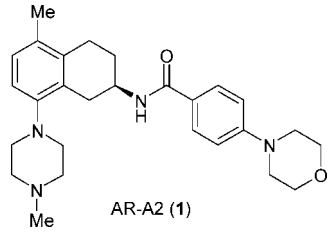


FIGURE 1. Structure of a novel CNS-active 5-HT_{1B} receptor antagonist.

aminase technology that managed to transform a parent tetralone to the corresponding amino-substituted moiety in high enantiomeric excess.[4] From a medicinal chemistry point of view, this was an excellent entry into an exciting field for further exploring the wider potential of a structural class that had demonstrated interesting clinical properties as CNS agents.[5] However, tempting this "shortcut" approach might have appeared, its value was limited by some rather serious drawbacks when considering large-scale synthesis of the target molecule.[6] The cost of the aminotetralin starting material was one prohibitive factor because the relatively premature state of the art for their preparation drove the price for bulk amounts up to astronomic levels ($50 000–100 000/kg).[7] Second, at the time, the underdeveloped technology did not offer access to a sufficiently large number of mutated enzymes that could be successfully applied to a wider range of substrates. This led to a situation where some aminotetralins were made easily and others were not made at all. Finally, a third restriction was the fact that in some cases only one of the enantiomers was obtained and not their antipodes.

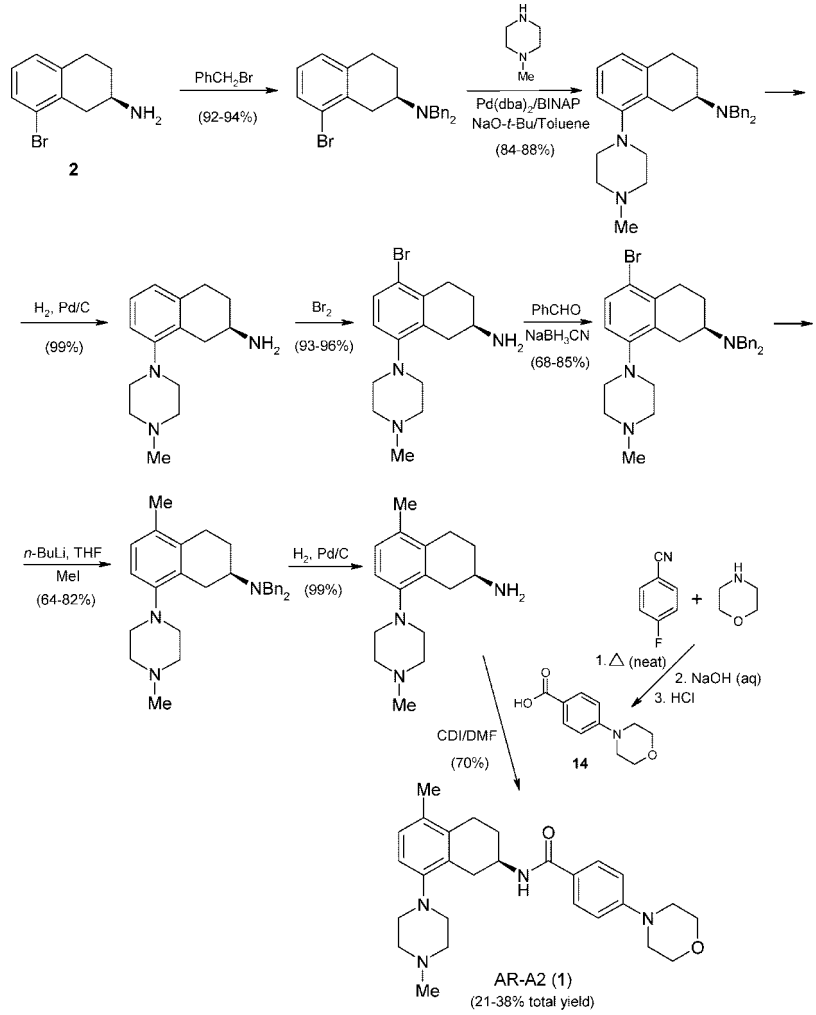
For discovery research, this meant that access to (*R*)-2-amino-8-bromotetralin (**2**) opened up avenues to a whole raft of modified target compounds that could be screened for receptor affinity and other crucial properties. Hence, the synthetic sequence designed on the basis of this concept was more of a generic one rather than focused on a specific target molecule, and this resulted in a route[8] of eight linear stages leading to **1** (see Scheme 1). The major disadvantage with this synthesis was undoubtedly the need to install the methyl group on the 5 position of the tetralin nucleus. This was executed according to a multistage procedure requiring aromatic bromination, amine protection, metallation/alkylation, and deprotection. These unattractive features coupled with the findings that in the lithiation/methylation step formation of the 5-*H* analogue was sensitive to the reaction temperature. Thus, already at −78 °C, sufficiently large amounts of this byproduct were formed to leave behind residual levels in the low percentage range even after chromatographic purification alongside a similar order of magnitude of the *n*-butyl derivative, traceable to the use of *n*-BuLi. Running at higher temperatures clearly supported this reaction outcome, which led to a more complicated chromatography and, concomitantly, a decrease in yield. From a technical feasibility point of view, this was seen as a considerable drawback given the difficulty to, first, ensure that a sufficiently low temperature is maintained during large-scale conditions and, second, the hard task to chromatographically separate these closely related analogues from the desired product. When these challenges were disregarded, a saviour of this route to making **1** could have been commercial accessibility to the 5-methyl analogue of **2**. However, the transaminase methodology of the supplier[7] failed to deliver the wanted (*R*) isomer **3** even after rigorous testing of numerous enzyme strains [although the (*S*) form could be obtained; see Scheme 2]. Another factor that had to be taken into consideration was the substantially lower water solubility of the 5-methyltetralone substrate, which, most likely, would have provided a negative impact on the productivity obtained from an enzymatic process operating in aqueous medium. With this analysis at hand, it was decided that the entire strategy based on purchasing the required aminotetralin stereoisomer as an advanced building block had to be abandoned. Notwithstanding this decision, a few hundred grams of AR-A2 were produced following the synthesis outlined in Scheme 1, inasmuch as the overall yield was in an indeed acceptable range of 21–38%. Fortuitously, this allowed for a positive response to the needs for a few hundred grams necessary to start further development work.

A Redesigned Route with Enhanced Synthetic Efficiency

When the synthesis adopted in early discovery was not used (Scheme 1), the task of making the desired product (**1**) had to undergo a *de novo* analysis from a retrosynthetic perspective. Thus, slight alterations in the bond disconnections of **1** compared to previously led to the identification of 3-methylphenylacetic acid (**4**) as a suitable starting point (Scheme 3). This approach addressed one of the most significant shortcomings of the first route, namely, that the methyl substituent would already be in place from the start, making the metallation–methylation protocol redundant. Similar to before, this new sequence made use of a tetralone (**6**) as a key intermediate and its formation was easily conceived in 2 steps from **4**: bromination followed by a Friedel–Crafts ring-closing alkylation with ethene as a reactant. The amino functionality was introduced using standard synthetic chemistry methods (as opposed to the use of an enzyme) via a reductive amination, and the racemic product obtained was subjected to a diastereomer resolution with D-tartaric acid. From there on, the remainder of the synthesis resembles the corresponding steps in the route described in the previous section. The layout of this novel sequence is shown in Scheme 3.

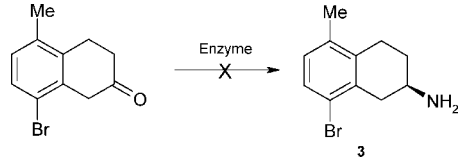
Some important features observed when developing this route warrant further discussion. In the first stage, acid **4**, commercially available in bulk amounts, is brominated using Br_2 in an aqueous system under basic conditions (K_2CO_3).[9] This procedure produces a mixture of mono-bromo regioisomers in a typical ratio between the 2-bromo-5-methyl (desired isomer, **5**)/4-bromo-3-methyl/2-bromo-3-methyl derivatives, respectively, of 4:2:

Scheme 1. First-Generation Route to AR-A2 (1) Applied by Medicinal Chemistry



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

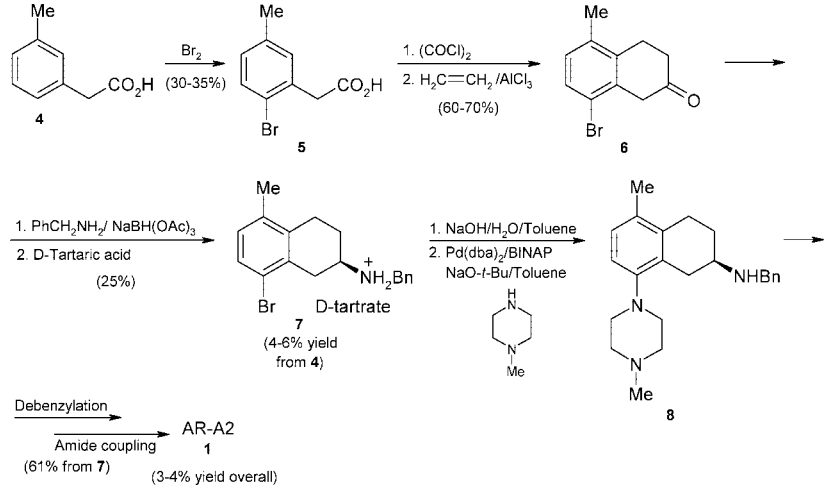
Scheme 2. Failed Approach To Produce the Desired Starting Material 3 Using an Enzymatic Method



1. Fortunately, the structural similarity of these components did not prevent an effective purification method to be developed, and therefore, two consecutive recrystallizations from water-based systems containing *i*-PrOH and HOAc managed to generate material (**5**)[10] in high purity (98%) at yields in the range of 30–35%. For process economy reasons, the loss of the bromo impurities residing in the mother liquor had to be investigated, and therefore, a recycling loop was devised that used a catalytic hydrogenation to regenerate starting material **4**. The second step is responsible for the formation of the tetralone core (**6**), and this was achieved in a rather straightforward manner via the acid chloride, which is then subjected to Friedel–Crafts conditions ($AlCl_3$) and ethene as the required C_2-alkylation equivalent.[11] Even when extensive efforts to optimize this reaction were allocated, the yields were always moderate and never exceeded 60–70%.

Proceeding with a smooth reductive amination,[12] where benzyl amine was used as a reactant, the racemic *N*-benzyl-2-aminotetralin was obtained in good yield, which, when subjected to diastereomer resolution, gave the (*R*) enantiomer isolated as the D-tartrate (**7**) in only 25% overall yield (50% of theory). This "classical" way of introducing the right stereochemistry into molecules has been the dominating technology when considering manufacture on large scale. A recent study[13] has again reconfirmed this picture, and thus, if those cases are ignored where the chirality is purchased from external sources (for example, chiral pool origin), then resolutions outweigh asymmetric methods by almost 3:1. Contrary to the situation when applying the Buchwald–Hartwig protocol[14] in the medicinal chemistry synthesis (Scheme 1), where the substrate was constituted by a tertiary amine (the dibenzyl derivative), the novel route contained a secondary amine functionality. The obvious reason for choosing this intermediary structure was the considerably improved atom economy offered by the elimination of a benzyl substituent (reduction in atomic "ballast" by ~21%), which

Scheme 3. Second-Generation Route to AR-A2: An Improved, Scale-up Friendly Synthesis of 1 That Requires Resolution of a Racemic Intermediate



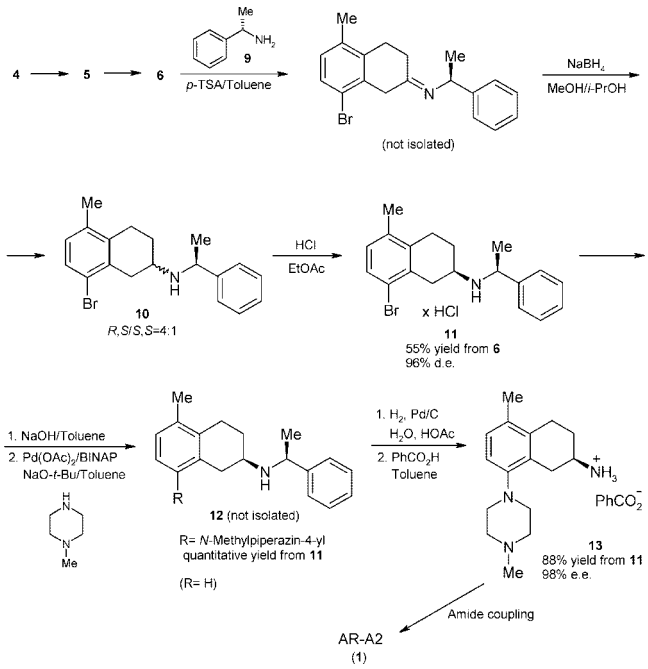
would notably reduce the weight of the material that needed to be processed. However, there was a fear that when using **7** as the free base this would risk generating a byproduct through intermolecular coupling (2-amino group of **7** attached to the aromatic ring of another molecule of **7**). Surprisingly, this side reaction did not occur, and therefore, the isolated product was exclusively composed of the wanted *N*-piperazinyl moiety **8** together with small amounts (<2%) of the **8**-*H* analogue. Our interpretation of this finding is that the Pd-catalyzed aromatic amination reaction is chemoselective because it discriminates between amines featuring different steric bias, giving preference to the least hindered moiety (*N*-methylpiperazine in this instance). As was the case in the first-generation route, the sequence is completed with a standard catalytic hydrogenation (Pd/C) followed by an amide formation to produce AR-A2 (**1**) using an overall shorter sequence. Scaling up the process based on the chemistry in Scheme 3 performed rather well, even if the total yield was only about 3%, and thus, it was possible to obtain 26 kg of product (**1**), which meant that, for example, the bromination step (**4** → **5**) was conducted as a single batch starting from 400 kg of phenylacetic acid **4** in a 6 m^3 reactor volume.

En Route to a Stereoselective Synthesis

In light of the experience gained from performing the sequence outlined in Scheme 3, it became apparent that, notwithstanding the technical operability and conciseness, the attributes with respect to capacity and cost were not sufficiently good. Thus, as the preliminary dose-finding studies, resulting in a projected daily intake of 100 mg/patient, indicated that in the event that AR-A2 made it to market, the annual volume of active compound would be in the range of multitons. The low efficiency obtained in the process from a yield point of view (~3%), especially in the late stage resolution where 75% of valuable material was lost, and without obvious opportunities for substantial improvements realized that yet another synthetic sequence would be needed. Arguably, the best way to respond to the shortcomings was to devise a method that allowed for the desired stereochemistry to be introduced via an asymmetric transformation. A re-evaluation of the current synthesis did not reveal new options that would dramatically improve the overall way that the target molecule was assembled. However, one opportunity was identified that would lead to a significant change in the efficiency of making AR-A2, namely, by introducing the *N* functionality by virtue of a chiral amine reactant as opposed to using an achiral alternative (benzylamine). When these ideas were translated into practice and the feasibility of this approach was confirmed with experimental studies, a third-generation process emerged. This turned out to be the optimum manufacturing procedure under the given circumstances, offering an entirely sufficient capability to deliver the product (**1**) in requested amounts and quality throughout the remaining lifetime of the project until its closure (see Scheme 4). A previously reported procedure[15] based on catalytic asymmetric hydrogenation of enamide substrates belonging to the bromo-2-aminotetralin family was actually evaluated in our case. The outcome was rather disappointing because application of the literature protocol, in line with the reported results,[15] generated **10** as a 1:1 mixture of diastereoisomers, rendering this methodology of little value for our purpose. Furthermore, in the event that this step had performed well, operating an amide-based strategy would most likely have led to complications later on in the sequence because the Buchwald–Hartwig step might suffer from the presence of an acidic proton on the amide nitrogen. Also, the removal of the acyl moiety on the 2-amino substituent poses a considerably tougher challenge, compared to running a catalytic hydrogenation used in the current process.

When benzylamine was changed to (*S*)-1-phenylethylamine (**9**) as the amino-group donator in conjunction with switching to somewhat modified reaction conditions (different reducing agent and solvent system), the crucial reductive amination step could be performed at a significantly better yield. Thus, in comparison to the poor

Scheme 4. Third-Generation Route: A Diastereoselective Synthesis of AR-A2 (1) Using (*S*)-1-Phenylethylamine (9) as a Crucial, Multitasking Component



outcome in the previous, resolution-demanding method, the new process offered more than twice the yield based on achieving a diastereomeric composition in the product mixture (**10**) after hydride reduction of (*R*,*S*)/(*S*,*S*) = 4:1.[16] Interestingly, the successful outcome relied to a large extent on performing the reaction in two stages: first, the formation of imine in a discrete transformation, followed by a separate reduction. If a one-pot procedure was applied, a 3:2 diastereoisomeric ratio was obtained, in favor of the desired product. Moreover, a literature report from the early 1990s[17] indicates that applying this synthetic methodology on a bromo-tetralone closely related to **6** using $NaBH_3CN$ in a mixture of MeOH and tetrahydrofuran (THF) (1:1) gave a completely racemic product in the form of a 1:1 ratio of diastereomers (no induction on C2). When this experimental protocol was tested on our substrate, a confirmative result was obtained, and it was only after modifying the solvent system and switching to $NaBH_4$ that a significant improvement in stereochemical purity was observed.

Despite investing considerable efforts optimizing the two-stage protocol, it was not possible to drive the outcome beyond a 4:1 ratio. It is not unlikely that this could, in fact, have been achieved, for example, by using chiral amines that display a higher degree of steric bias (e.g., 2-naphthylethylamine) or by screening for alternative reducing agents. At the time, however, the choice of (*S*)-1-phenylethylamine as a reactant/auxiliary was seen as an excellent compromise by virtue of its availability on large scale at an acceptable price, its compatibility with the conditions applied in the succeeding step (Buchwald–Hartwig coupling), and finally, its easy removal at the end of the three consecutive stages. After this novel method was introduced, the capacity of the process for making AR-A2 underwent a step change and, overall, >600 kg of the HCl salt **11** was manufactured in a highly reproducible way at a consistent quality level [~96% diastereomeric excess (de)].

Focusing on how to best conduct the attachment of the piperazine moiety to the aromatic ring, the obvious starting point was to revert to the method that had been successfully used in the previous approach (Scheme 3). Surprisingly, a mere translation of this protocol to the current substrate (**11** as a free base) resulted in an increased formation of the **8**-*H* analogue (**12**, R = H). On the pilot-plant scale, the amount rose to as much as 11% in the worst case, and alongside, generating this highly undesirable byproduct, the Pd catalyst precipitated out of the reaction mixture as a brown solid material (Scheme 4). It was obvious that the way of running this step would have to undergo a profound re-assessment and redevelopment to obtain optimum conditions. Numerous experiments were carried out to reach the goal, and this meant evaluating several parameters, foremost of which was finding the best combination of catalyst and ligand for this particular system. As it turned out, $Pd(OAc)_2$ was confirmed as the better choice for performing the desired reaction compared to the dba complex initially applied. Furthermore, this switch was judged to be convenient also from a large-scale perspective, as witnessed by lower cost and easier handling of $Pd(OAc)_2$.

The crucial task of identifying the most effective ligand for this particular transformation was addressed from the basis of the known state of the art.[14a–c] Thus, at the time of conducting this investigation around the year 2000, the "gold standard" used in these types of aromatic aminations was the renown [1,1′-binaphthalene]-2,2′-diylbis-[diphenylphosphine] (BINAP), either in enantiomerically pure form or as the racemate. In our screening studies, this chelating ligand was compared to others that had been designed more recently but the results were unambiguous in pointing out BINAP as being superior. It was also shown that the form in which BINAP was applied, enantiopure versus racemic, had no effect on the performance of the reaction. The final conclusion was that (*R*)-BINAP constituted the optimal alternative under the current circumstances by virtue of its availability in bulk quantities. One of the key findings made during the course of our experiments was the pronounced influence exerted by the BINAP/$Pd(OAc)_2$ ratio on the formation of the **8**-*H* analogue (**12**, R = H). With <2 mol equiv of ligand over the Pd catalyst, this byproduct was produced in 11%, whereas an increase of BINAP to 4 mol equiv or more drastically reduced the amount to 0.5% or below (see Table 1 for examples of how different experimental setups influenced the result). The conclusions drawn from these data are (i) BINAP constitutes the best ligand (entries 2 and 3); (ii) racemic versus enantiopure BINAP is of no importance (entries 1 and 10); (iii) the choice of base is crucial (entries 4 and 5); (iv) the reaction tolerates up to 0.06% H_2O (entry 7); and (v) changing of solvent from

Table 1. Key Experiments for the Buchwald–Hartwig Coupling

entry	altered conditions[a]	product **12** after 3 h (% GC)	**8**-*H* analogue after 3 h (% GC)	remarks
1	rac-BINAP as the ligand	99	0.3	
2	Xantphos as the ligand	62	7	
3	(*o*-tol)$_3$P as the ligand	18	14	xylene at 130 °C
4	NaOMe as the base	10	6	
5	NaOEt as the base	0	0	
6	xylene at 130 °C	99	0.7	<30 min to full conversion
7	0.1 equiv (=0.06%, v/v) of H_2O	99	0.7	
8	1.4 equiv of BINAP to $Pd(OAc)_2$	88	11	
9	2 equiv of BINAP to $Pd(OAc)_2$	96	3.1	
10	5 equiv of BINAP to $Pd(OAc)_2$	99	0.3	

[a] Normal conditions are 1.0 equiv of **11** 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 °C. The crucial BINAP/$Pd(OAc)_2$ ratio is, thus, set at 4.25:1. Listed in the table are deviations from this experimental protocol.

toluene to xylene has only a marginal effect on the yield but significantly accelerates the rate of the reaction (entry 6).

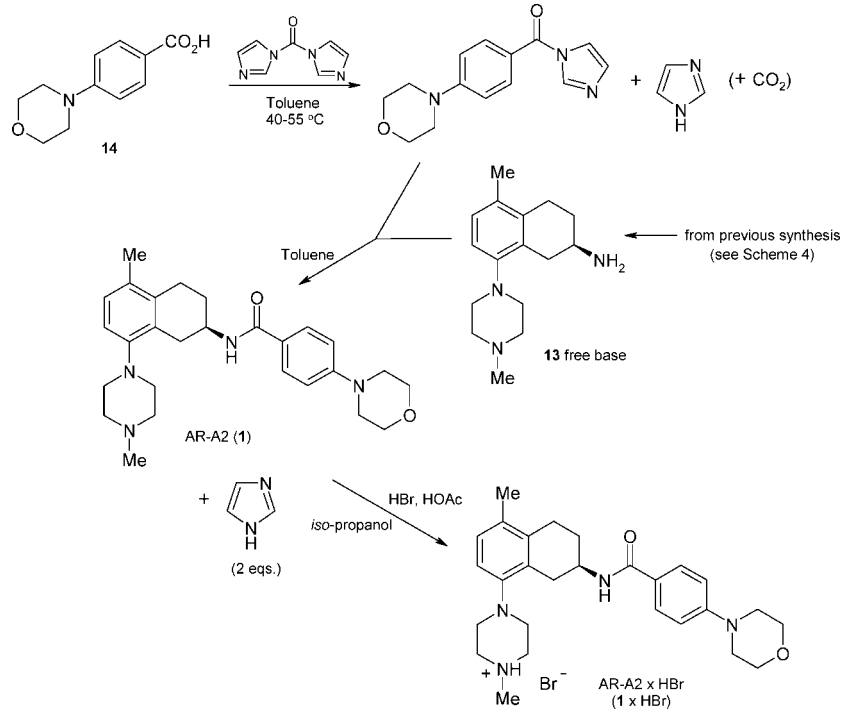
Furthermore, when different protocols were scrutinized for the best practical way of running this step, it became clear that the premixing of $Pd(OAc)_2$, BINAP, and methylpiperazine was critical to achieve a successful outcome. The rationale for this observation was that adhering to such a procedure enabled a stable form of the active catalyst to be generated prior to initiating the reaction. Once this catalytic complex was formed, the behavior was very user-friendly as displayed by its high degree of stability in air alongside an insensitivity to water at levels up to almost 0.1% (v/v). On a scale-up to the pilot plant (2500 L), the process thus developed was robust and reproducible as confirmed by consistently achieving a quantitative conversion of the starting material (**11**) within 4 h at 100 °C. After workup (aqueous acidic extraction), product **12** was obtained in quantitative yield (as measured in the process stream taken forward to the next step without isolation) with superb quality (<0.5% **8**-*H* byproduct) at a maximum batch size of 125 kg.

The final stage of the three consecutive steps required to prepare **13**, the final intermediate in the total synthesis, was the deprotection of the amino functionality by cleaving off the chiral auxiliary. This seemingly trivial transformation widely applied in organic chemistry is frequently conducted under reductive conditions using a metal catalyst, notably Pd on charcoal.[18] To define the best mode of operation suitable for substrate **12** (Scheme 4), a set of about 10 different grades of Pd catalysts were screened together with a range of solvents. Initially, it was found that the reaction worked well using "standard" Pd/C (of type 87L[19] with 10% Pd content) at a H_2 pressure of 5 $\times$ 10^5 Pa (5 bar) in toluene. However, when this approach was tested on a larger scale (20 kg of **12** in 600 L), it was noticed that the product (**13** as the free base) had a tendency to precipitate out of solution in the form of a thick syrupy oil, which complicated the sampling procedure and reduced the reaction rate. Moreover, impurities accumulated from previous steps led to cross-contamination and caused poisoning of the catalytic species, and this had to be counteracted by adding the catalyst in two or three aliquots. Switching from toluene to an entirely aqueous system in the presence of some acetic acid was shown to offer considerable advantages. Thus, when the reaction under these circumstances was run in combination with using a different Pd/C catalyst (type 37[19] with 5% Pd), the H_2 pressure could be significantly reduced (from 5 $\times$ 10^5 to 3 $\times$ 10^5 Pa) and full conversion was reached within 3–5 h compared to 12–36 h when applying the previous protocol. In this case, precipitation of an oily material did not occur, and instead, the desired product (**13**) could be isolated as a crystalline, easily filtrated salt after extraction into an organic phase (toluene) followed by the addition of benzoic acid in *iso*-propanol. Important in this context was the fact that the catalyst could be effectively separated off via filtration, thereby guaranteeing that hardly any residual amounts of heavy metal would be left in the mother liquor. Further scale-up of this one-pot deprotection method demonstrated a good robustness and reproducibility, eventually leading to the successful manufacture of 110 kg of **13** corresponding to a yield of 88%.

The End-Game: Completion of the Synthesis

Succeeding in developing a synthesis whose core part, the installment of the required stereochemistry, outperformed the first-generation method (Scheme 3) by at least a factor of 2, it remained to complete the sequence via the formation of an amide bond and, subsequently, precipitating the target molecule in its final form as the mono-HBr salt. Initially, the method applied for the amide coupling originated from medicinal chemistry, where DMF had been used as a solvent in the reaction in combination with CDI as a condensing agent. This procedure, unfortunately, resulted in a poor yield (50%) because of the loss of material in various process streams (notably in the DMF-containing H_2O phase) during the complex workup that, among other things, required a slurry wash (in MeOH) of AR-A2 base as a means of improving the purity. A further poignant weakness was the inability to perform the salt precipitation in an integrated fashion without prior isolation of the free base (as a MeOH solvate). Evaluation of different options showed that shifting to toluene was ideal because the yield in the amide-forming step was not only higher but it also allowed for the crystallization of the AR-A2 $\times$ HBr product

Scheme 5. Final Steps in the Synthesis of AR-A2 × HBr, where the Use of CDI as Condensing Agent Enables the Precipitation of the HBr Salt from a Suitably Buffered System



in a one-pot scenario. Thus, activation of the 4-morpholinobenzoic acid[20] (**14**) side chain (prepared as depicted in Scheme 1 with yields ≥96% in the pilot-plant scale) by using CDI at slightly elevated temperatures (∼50 °C) and subsequently adding aminotetralin **13** (after conversion to the base form) generated the desired product (**1**) in a crude state, which immediately could be transformed into the final hydrobromide. A spin-off achieved when operating the process along these lines was the elegant reuse of the imidazole moiety released as a byproduct from the CDI reagent, which is in stark contrast to previous methods (Schemes 1 and 3), where imidazole had to be added separately. This imidazole amount (2 equiv formed during the course of the reaction) constituted an ideal and perfectly suited buffer system in the present case, as demonstrated by the ability to selectively generate the wanted mono-HBr compound (**1** × HBr) as the sole product obtained after crystallization (see Scheme 5). The three basic nitrogen atoms in the parent molecule **1** (located in the piperazine and morpholine rings, respectively) spanning a pK_a range of roughly 2–8, are sufficiently similar to allow for at least the formation of a di-HBr salt under nonbuffered conditions. In the presence of imidazole, however, only the most basic nitrogen, the N^4 position of piperazine, is protonated. Upon scale-up, the overall performance of this step was excellent, offering a yield of about 76% at a batch size of 72 kg. The active pharmaceutical ingredient AR-A2 × HBr thus produced met the stringent quality requirements, for example, an enantiomeric purity of ≥99 % (*R*), to gain approval for clinical studies in humans.

Conclusions

In this case story, the entire chain from the earliest attempts to synthesize the target compound AR-A2 via a first-generation process to the finish where a manufacturing method of commercial quality was at hand has been covered. The various scales at which these different syntheses were operated (hundreds of grams, tens of kilograms, and hundreds of kilograms) give good evidence of the capacity inherent in each of the procedures and what steps are required to take a method from laboratory to plant. Although, when the route devised by medicinal chemistry is performed at an acceptable overall yield of >20%, it (Scheme 1) was quickly abandoned because the cost of the aminotetralin starting material made AR-A2 unsustainably expensive. Two commercially viable routes were taken forward, and the improvements obtained in the synthesis of AR-A2 is substantiated by the overall yield delivered by the final process (Schemes 4 and 5), which was about twice as high as in the version initially scaled up (Scheme 3), 7% compared to 3–4%. A key feature in all of synthetic organic chemistry is the number of steps required to make a given molecule and for AR-A2, with its rather complex architecture, this translates to not more than 10 (which includes the making of the side chain). From a processing point of view, however, the number of isolations that need to be carried out along the route of synthesis is of even higher importance, and therefore, the total number of only four truly isolated stages [**5**, **11**, **13**, and **1** (excluding the final product AR-A2 × HBr)] gives a clear indication of the excellent efficiency that was achieved. Finally, with a large portion of drug compounds being chiral, efficient methods for their preparation in

high enantiomeric purity are essential.[13,21] For AR-A2, this meant using (*S*)-1-phenylethylamine as a crucial component in the construction work, where the stereogenic center was installed using a diastereoselective hydride reduction protocol running at 96% de.

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