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Development of an Enantioselective, Kilogram-Scale, Rhodium-Catalysed 1,4-Addition

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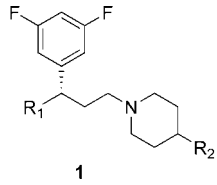
Abstract:

A rhodium-catalysed 1,4-addition of an arylboron species to an α,β-unsaturated ester was the key chirality-inducing step in the synthesis of an API. We describe herein the development of this chemistry, including optimization of reagent charges, reaction conditions, and metal recovery, in order to allow manufacture at multikilogram scale. A key result was the unexpected discovery that the use of a minimal quantity of an alcohol, rather than water, reduces the extent of rhodium-mediated protodeboronation of the boron species. This allowed the charge of this expensive reagent to be significantly reduced. Furthermore, the use of an alcohol instead of water avoided the agglomeration of the inorganic base present in the reaction, making the process more robust and operationally simpler. To our knowledge this is the first time that this type of C−C bond-forming chemistry has been used in a multikilo manufacture.

Introduction

Two related series of compounds with the general structure (**1**) were required as part of a drug development program.



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R_1 = aryl or *N*-functionalised piperidin-4-yl
R_2 = a wide range of functionality

Our colleagues in Medicinal Chemistry had successfully made the first gram quantities of material **1** using the chemistry shown in Scheme 1. The key step in this synthesis utilised an ephedrine-based chiral auxiliary to control the facial selectivity of a copper-mediated 1,4-addition of an aryl-Grignard.

However, we felt that the rhodium-catalysed 1,4-addition of an arylboron species to an unsaturated ester offered a more efficient way of introducing the required chirality, using a disconnection which would readily accommodate potential variation in the structural series (Scheme 2)[1,2] In addition, this approach would avoid the generation of copious quantities of copper-contaminated waste, eliminate the need to use the expensive Bu_2BOTf reagent, and remove the need for a chiral auxiliary that may not be recyclable. Furthermore, the rhodium-mediated chemistry would also avoid both low temperatures (−70 °C) and the need to obtain ephedrine which is subject to controlled-substances legislation in the U.K.

Results and Discussion

We first applied this chemistry to a series of compounds where R_1 in Scheme 2 was an aryl group. This work and the identification of a previously unreported 1,3-addition product **2** (Scheme 3) will be reported elsewhere.[3]

After working on this initial series our attention turned to a second series of compounds where R_1 = 1-mesylpiperidin-4-yl. In this case a different unsaturated ester **3** was required as the substrate for the key 1,4-addition chemistry. This was synthesized using the chemistry shown in Scheme 4. Thus, ethyl isonipecotate was mesylated using standard conditions to give ester **4**. Ester **4** was reduced to the alcohol **5** using lithium aluminium hydride, and then partially reoxidised to the aldehyde **6** via a Swern oxidation. A direct reduction of the ester **4** to the aldehyde **6** using DIBAL was investigated but was found at this time to give unrealiable and unacceptable levels of over-reduction to the alcohol **5**: the best ratio achieved was 2:1 in favour of the aldehyde **6**. In fact, the aldehyde **6** was found to be difficult to handle, forming what were presumed from mass spectroscopy data to be dimers (**7a** or **7b**) via aldol-type chemistry, as well as a cyclic trimer **8** in protic solvents (Figure 1). Consequently the aldehyde **6** was not isolated but was reacted in situ with the mono-*iso*-propyl malonate **9**, itself prepared in solution by the reaction of *iso*-propanol with Meldrum's acid (**10**). After heating to effect decarboxylation, this gave the unsaturated ester substrate **3** for our key chirality-inducing, 1,4-addition step.

We also investigated the synthesis of **11** from the cheaper ethyl isonicotinate (**12**) (Scheme 5). However, no desired product **13** was detected from the key 1,4-addition reaction of the arylboron with substrate **14**. We believe this to be because the substrate **14** coordinates to the rhodium atom via the pyridine nitrogen atom, removing the metal from the catalytic cycle. In support of this hypothesis we also found that we needed to carefully control the level of piperidine present in **3** (Scheme 4) as high levels of this amine also resulted in catalyst poisoning in the subsequent step.

In contrast to our earlier work on cinnamate derivatives (Scheme 3),[3] when the key 1,4-addition reaction was first tried on the new substrate **3** using the conditions shown in Scheme 3 there was no aryl insertion detected at the α-position, and quantitative solution yield of the desired product in ∼90% ee

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(1) Hayashi, T. *Synlett* **2001**, 879–887.
(2) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
(3) Williams, A. J.; Parker, A. J. Manuscript in preparation.

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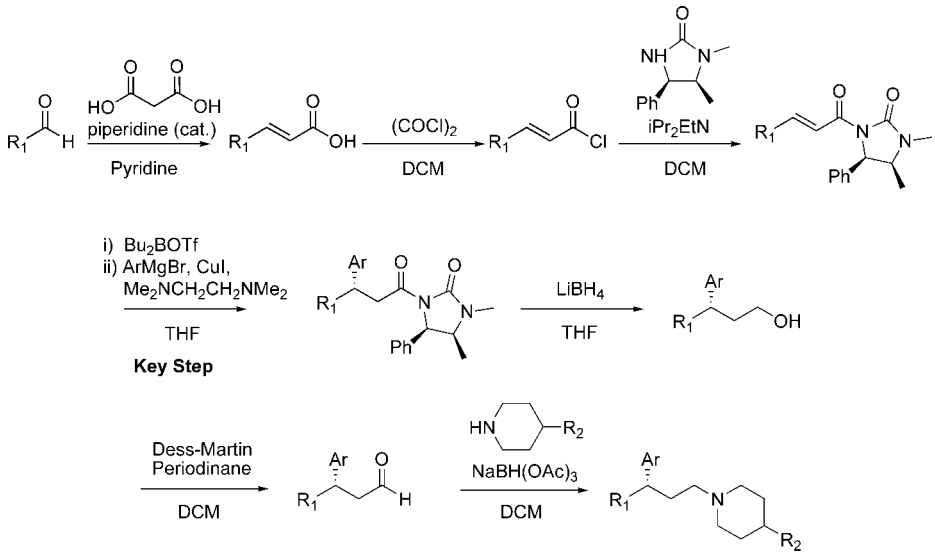
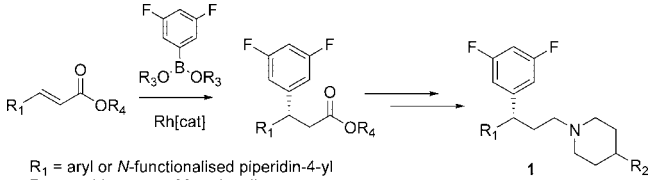
Scheme 1. **Medicinal Chemistry route**



Scheme 2. **Proposed alternative route**



R_1 = aryl or *N*-functionalised piperidin-4-yl
R_2 = a wide range of functionality
R_3 = H or alkyl
R_4 = alkyl

was achieved. However, as well as further improving the ee, there were several issues that required resolution in order to provide larger quantities of material:

- The initial conditions required the use of 3.5 mol equiv of neopentyl 3,5-difluorophenylboronate ester, which was found to be a very expensive starting material (£5600/kg for 1 kg). Most of this boronate ester was wasted via rhodium-mediated hydrolysis to difluorobenzene (vide infra).[4,5]
- The mixture of inorganic base and water used in the initial conditions resulted in a coating of solid on the vessel walls and agglomeration of solid into large lumps within the reaction mixture—clearly undesirable for scale-up.
- The removal of neopentyl glycol-related species from the product.
- The presence of rhodium in the product at an unacceptably high level (typically ~200 ppm).

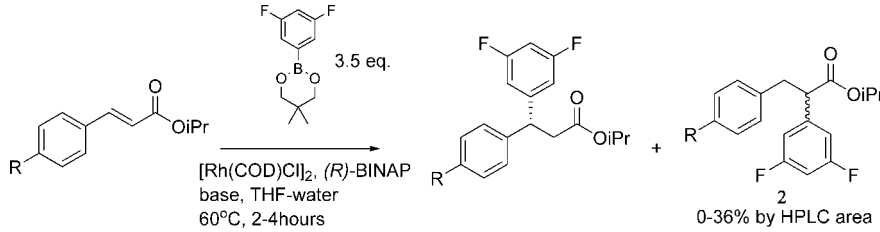
The first three issues were solved by a combination of several changes: the use of iPrOH in place of water, the use of K_2CO_3 in place of K_3PO_4, and the use of 3,5-difluorophenyl boronic acid (**15**) in place of the corresponding neopentyl glycol ester (Scheme 3).

3,5-Difluorophenyl boronic acid (**15**) was approximately one-seventh the price of its neopentyl glycol ester (£750/kg compared to £5600/kg at the time of this work). In addition, use of the boronic acid eliminated the need to prepare the boronate ester as part of the manufacture, thus increasing the overall efficiency, as well as avoiding the need for the technically difficult isolation of the product from neopentyl-based byproduct of the process. The neopentyl boronate ester had initially been used because it was commercially available, and it had showed promise in an early screen of available 3,5-difluorophenyl boronate species (boroxine, boronic acid, and boronate esters) with the initial series of compounds where R_1 = aryl (Scheme 3). However, it was demonstrated that the reaction also proceeded well with 3,5-difluorophenyl boronic acid (**15**) or with the corresponding boroxine (**16**) (Scheme 6). In fact, it was later found that some commercial supplies of "boronic acid" actually contained a significant proportion of boroxine, and further work on the impact of this is ongoing.

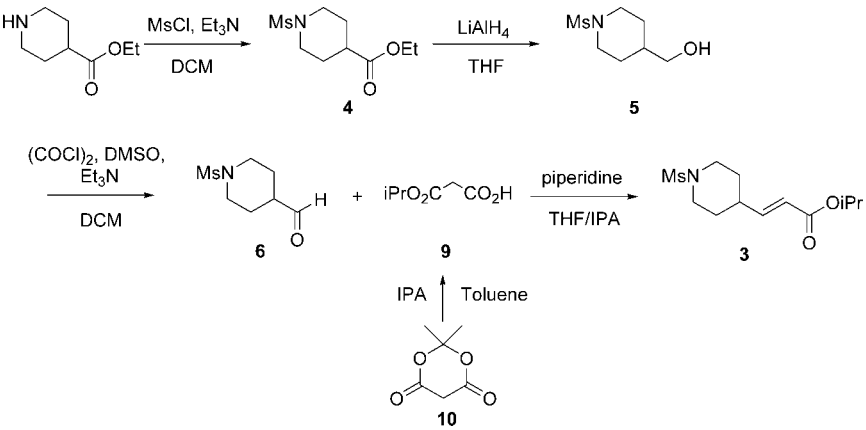
A catalytic quantity of K_3PO_4 was sufficient for the boronate ester-based reaction, but a stoichiometric charge of K_3PO_4 was required, as might be predicted from the proposed mechanism (Scheme 7), when using the boronic acid (**15**). However, this increased amount of K_3PO_4 made the issues associated with the nonhomogeneity of the reaction even more marked. A switch from K_3PO_4 to K_2CO_3 was made, because the latter is more readily available in a finely ground form ("325 mesh") which was found to be beneficial on scale-up. A further key result was the discovery that the use of a small amount of an alcohol in place of water allowed the finely divided K_2CO_3 to remain uniformly suspended throughout the reaction, rather than settling in lumps at the bottom of the reactor and coating the reactor walls. Although not an issue on a small scale, the physical behaviour of the base became very important on scale up, when the rate of reaction was found to be unacceptably slow using a water-based system.

(4) Senda, T.; Ogassawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852–6856.
(5) Boiteau, J-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681–684.
(6) (a) See for example: Amengual, R.; Michelet, V.; Genêt, J.-P. *Synlett* **2002**, 1791–1794. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058. (c) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944–8946. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951–5955. (e) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580. (f) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047–4056. (g) Navarre, L.; Pucheault, M.; Darses, S.; Genet, J-P. *Tetrahedron Lett.* **2005**, *46*, 4247–4250. (h) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285–2288.

Scheme 3. **Identification of 1,3-addition product 2**



Scheme 4. **Synthesis of substrate 3 for rhodium-catalysed 1,4-addition**



To date there are many examples of rhodium-catalysed 1,4-additions to unsaturated esters, ketones, amides, and analogues thereof in the literature.[6] In these publications an excess of boron species is used (2 equivalents or more—sometimes as much as 10 equivalents) due to the competing rhodium-mediated protodeboronation of the boron species under the process conditions (Scheme 7). It is postulated that the mechanism of protodeboronation involves an aryl-rhodium species being intercepted by a molecule of water or alcohol to form the corresponding arene. Following the reactions by ^{19}F NMR[7] enabled us to show that the extent of rhodium-mediated protodeboronation of 3,5-difluorophenyl boronic acid is less in the presence of an alcohol than in the presence of water (Figure 2). Thus, the use of a minimum amount (<2 equiv) of *iso*-propanol instead of water allowed the charge of 3,5-difluorophenyl boronic acid, still representing the highest proportion of the cost of raw materials in this manufacture, to be reduced from 3.5 equiv to 1.35 equiv. *iso*-Propanol was chosen to avoid any possible transesterification of the ester group during the reaction. This key discovery[8] should be applicable to other rhodium-catalysed 1,4-additions to different substrates.

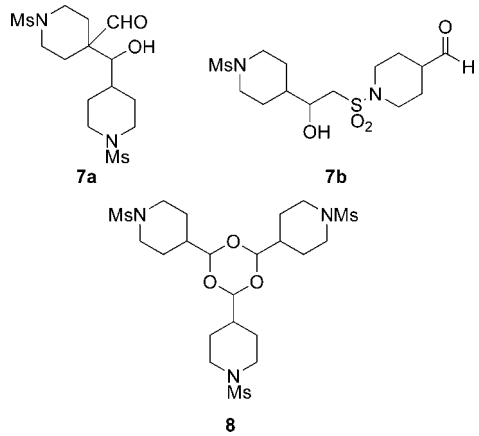


Figure 1. **Proposed structures of impurities. Protodeboronation of 3,5-difluorophenyl boronic acid.**

It was thought that the steric bulkiness of the ester group might affect the ee. Thus, the ethyl and *tert*-butyl ester analogues of **3** were synthesized and subjected to the standard reaction conditions (Scheme 8).

These reactions all proceeded to completion, and the ee's were 37, 90, and 92% for the ethyl, *iso*-propyl, and *tert*-butyl ester substrates, respectively. However, the *tert*-butyl substrate reacted much more slowly than the *iso*-propyl variant (>24 h vs 2–4 h for the *iso*-propyl substrate) which could mean that a greater proportion of the boronic acid reagent would degrade via protodeboronation during the reaction. Thus, the optimal balance between ee and reaction rate could be achieved by using the *iso*-propyl ester. The ee was further optimised to >99.5%

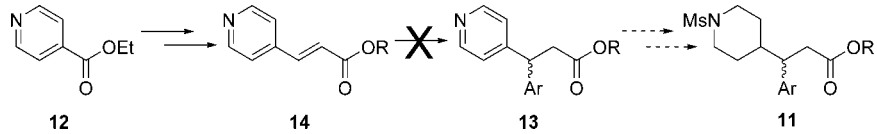
(7) 3,5-Difluorophenyl boronic acid was charged to a small volume reactor (4 mL capacity). Finely ground potassium carbonate (7.5 mol%) and trifluoromethylbenzene (~0.3 mol equiv, used as an internal standard) were charged before dissolving the mixture in anhydrous THF and adding either water or *iso*-propanol (1.5 mol equiv). A catalyst solution of [Rh(COD)Cl]$_2$ (0.015 mol equiv) and (*R*)-BINAP (0.037 mol equiv) was prepared and allowed to completely dissolve and then stand under a nitrogen atmosphere for 10 min before use. A diluent stock solution comprising of DMSO-d_6 (10 mL), acetic acid (500 μL [to quench the reaction]) and trifluoroacetic acid (5 μL [internal reference for the ^{19}F NMR]) was prepared in a 100 mL volumetric flask and made up to the mark with DMSO (nondeutrated). This stock solution was used to dilute the reaction samples (see below). The reaction was heated to 60 °C and maintained at that temperature throughout the course of the reaction. At set intervals, samples were removed (20 μL) and diluted with the DMSO stock solution (980 μL). The sampling times were 0, 15, 30, 60, 120, 180, 240, 300, 360, 420, 480, 600, 720, 840, 960, 1200, and 1440 min.

(8) Williams, A. J.; Patel, I.; Oldfield, J. Int. Pat. Appl. WO2007/057643, 2007.

(9) Smopex-234 is commercially available for GMP manufacture from Johnson-Matthey (http://www.smopex.com) who can also arrange for metal recovery from reaction residues.

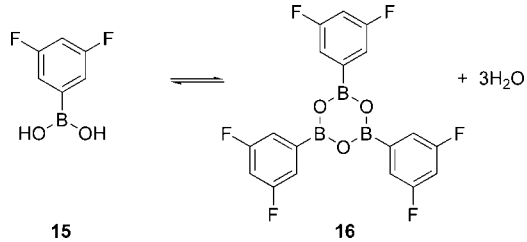
(10) Bunten, K. A.; Farrar, D. H.; Poë, A. J.; Lough, A. *Organometallics* **2002**, *21*, 3344–3350.

Scheme 5. **Attempted alternative synthesis**



12 14 13 11

Scheme 6. **Interconversion of boronic acid and boroxine**



15 16

by ensuring that the catalyst precursor, $[Rh(cod)Cl]_2$, and the phosphine ligand were premixed for a sufficient time before addition of the other components of the reaction.

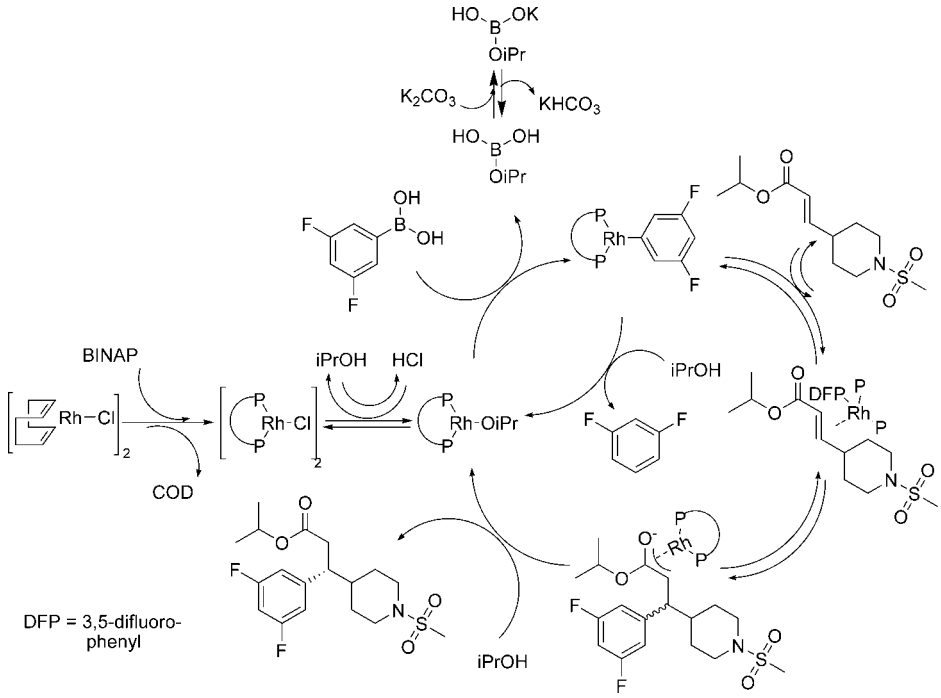
The final issue that required resolution before scale-up was the removal of rhodium to an acceptable level in the product. In earlier manufactures, rhodium levels in the ester (**17**) were typically >200 ppm and were not significantly reduced during downstream processing to the final API. For the initial manufacture of three batches, each giving around 3 kg of ester product (**17**), a wash of an organic solution of the product with aqueous cysteine was chosen as a cheap and readily available method of rhodium removal. However, this still gave product containing 60–90 ppm rhodium, which was only acceptable for very early toxicology studies.

Subsequent to this first manufacture, further rhodium removal methodologies were investigated. Using our Zymark robotic system, twenty-two commercially available rhodium scavengers were added to a reaction solution that had achieved the required 1,4-addition. These samples were heated to 60 °C for 20–24 h and sampled for rhodium-content by XRF at various times. All the scavengers demonstrated at least some capacity to adsorb rhodium, but Smopex-234 was chosen for further development because of its low cost relative to the others and because it is approved for use in GMP manufacture.[9]

A laboratory reaction to test Smopex-234 on a slightly larger scale was carried out. Unexpectedly the rhodium content of this reaction mixture after treatment with Smopex-234 was significantly higher than in the corresponding robot reaction. Similarly, in the earlier reactions when cysteine had been used for rhodium removal, it had also been found that the rhodium content was higher when the reaction was done on 3 kg scale than it had been on a smaller scale in normal laboratory glassware. So it seemed that rhodium removal was generally less efficient on a larger than on a smaller scale.

A possible reason for this was that the smaller-scale reactions were less well inerted in both cases. On the robot the reaction itself had been carried out under inert conditions, but the Smopex-234 treatment had not, whereas both stages of the comparable laboratory experiment had been rigorously inerted. Similarly, it is often found that inertion improves on scale-up, and this could explain why rhodium removal was less efficient using cysteine on the 3-kg scale than in the laboratory. It is postulated that exposure to oxygen may cause oxidation of the BINAP ligand,[10] which could release the metal into solution and facilitate its removal by either cysteine or Smopex-234. Alternatively, the physical removal of the insoluble oxidised BINAP−rhodium complex by filtration may contribute to lower

Scheme 7. **Proposed mechanism**



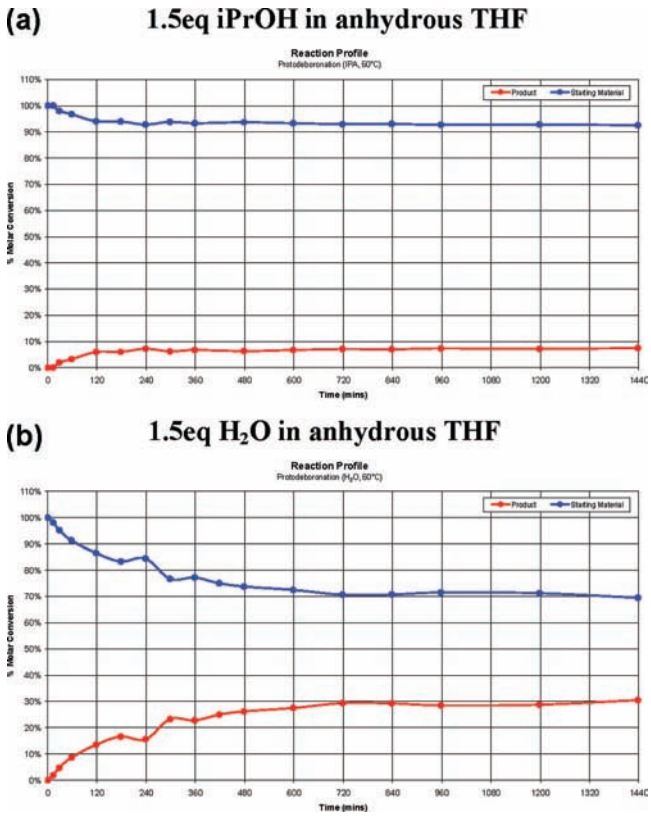
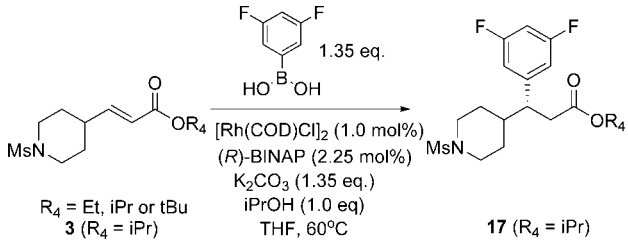


Figure 2. **Protodeboronation of 3,5-difluorophenyl boronic acid.**

Scheme 8. **Standard reaction conditions**



levels of rhodium in the product, or the oxidant may change the oxidation state of the metal and facilitate its removal from solution.

At AstraZeneca the Basis of Safety for plant operation typically relies on the exclusion of oxygen from the presence of flammable materials. Hence an alternative oxidant to atmospheric oxygen was required to aid rhodium removal. The effect of a variety of oxidants on the removal of rhodium from the THF reaction solution was examined. After completing the 1,4-addition, reactions containing mCPBA, MnO_2, NBS, NCS, Oxone, H_2O_2, and NaOCl were stirred for 1 h before Smopex-234 was added. These reactions were compared to two control reactions: one with no oxidant, and the other with no oxidant and no Smopex-234. In many cases the addition of oxidant caused an immediate change from deep red to pale yellow/orange, a colour change that is associated with catalyst deactivation. The lowest level of rhodium was achieved using Oxone, and so the combination of this with Smopex-234 was further investigated, varying the temperature and loading of the Smopex-234 resin to finally optimise rhodium removal. When these reaction and workup conditions were applied together and scaled up to two batches each starting with 27 kg of substrate (**3**), the rhodium level in the product (**17**) was consistently <30 ppm, which translated to well below our 10 ppm target for the final API. Careful rhodium tracking during the manufacture showed that 99.6% of the input rhodium can be accounted for, with 97% being removed by the combination of Oxone and Smopex-234. In addition the Smopex-234 can be returned to the supplier for rhodium recovery.

Conclusion

A rhodium-catalysed enantioselective 1,4-addition has been scaled up to provide more than 50 kg of product (**17**) in two batches, in an average yield of 74%, not including the material lost to the filtration "heel". The product had an assay of 99% and contained less than 0.5% w/w of the undesired enantiomer and the rhodium content was <30 ppm. Thus, the applicability of this powerful C−C bond-forming methodology has been demonstrated on a kilogram scale for the first time within AstraZeneca. Several changes to previously published procedures have been incorporated in order to make this reaction more amenable to scale-up. Most significantly, these changes involved: the use of an alcohol instead of water to enable minimization of the charge of expensive boron species and to improve the "form" of the reaction suspension; and the use of an oxidant to facilitate removal of rhodium from the product. These changes should be generally applicable to this reaction with other substrates.

Experimental Section

General. Starting materials, reagents, and solvents were obtained from standard commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker-400 instrument. Reaction progress was followed either by GC (using an Agilent 6890N GC, fitted with a DB-5 column with dimensions of 30 m × 0.32 mm and 1 μm particle size, and using a temperature profile from 150 to 325 °C at 25 °C/min) or by LC (using an Agilent 1100 LC, fitted with a ThermoElectron Betabasic 18 column with dimensions of 15 cm × 4.6 mm and 3.5 μm particle size, and eluting with a solvent gradient from 35% to 95% of MeCN/water containing 0.1% formic acid over 10 min).

Preparation of 1-Methanesulfonyl-4-(ethoxycarbony1)-piperidine (4). Ethyl isonipecotate (1 mol equiv) was charged to a reaction vessel followed by a line wash of DCM (1 rel vol). Triethylamine (1 mol equiv) was charged to the vessel followed by a line wash of DCM (1 rel vol). DCM (5 rel vol) was charged to the vessel and the reaction mixture cooled to between 0 and 5 °C. A solution of methane sulfonyl chloride (1 mol equiv) in DCM (2 rel vol) followed by a line wash of DCM (1 rel vol) was added to the vessel while maintaining the temperature between 1 and 10 °C. The reaction mixture was stirred at between 0 and 10 °C until the reaction was complete. Purified water (5 rel vol) was charged and the reaction mixture was stirred for 15 min at between 5 and 10 °C. The resulting phases were separated and the organic phase was concentrated to approximately 4.5 rel vol by atmospheric distillation. The concentrate was clarified, and then di-*iso*-propylether (10 rel vol) was added and the reaction concentrated

again to approximately 4.5 rel vols by reduced pressure distillation. Another portion of di-*iso*-propylether (10 rel vol) was added and the resulting suspension was stirred at ambient temperature for at least 60 min. The solid was isolated by filtration, washed with di-*iso*-propylether (2 rel vols) and then dried at ambient temperature to give the title compound in approximately 93% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.05 (q, J = 7.1 Hz, 2H), 3.46 (d, J = 12.0 Hz, 2H), 2.81 (s, 3H), 2.76 (t, J = 11.5 Hz, 2H), 2.48 – 2.38 (m, lH), 1.90 (d, J = 13.3 Hz, 2H), 1.56 (dd, J = 35.4, 3.5 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H).

Preparation of (1-Methanesulfonylpiperidin-4-y1)methanol (5). 1-Methanesulfonyl-4-(ethoxycarbony1)-piperidine (**4**) (1 mol equiv) was charged to a reaction vessel followed by a line wash of THF (6 rel vols). The reaction mixture was cooled to between 0 and 10 °C. A solution of lithium aluminium hydride (1 M in THF, 0.75 mol equiv) followed by a line wash of THF (1 rel vol) was added to the vessel, keeping the temperature between 0 and 20 °C, and then the reaction mixture was warmed to ambient temperature and stirred until the reaction was complete. The reaction mixture was cooled to between 0 and 2 °C. Purified water (1 rel vol) was then charged to the vessel maintaining the temperature between 0 and 10 °C. The pH of the reaction was adjusted to <2 by charging 5 M HC1, maintaining the temperature between 0 and 10 °C. The reaction mixture was warmed to room temperature and stirred for at least 15 min; the phases were then separated. DCM (5 rel vol) was charged to the aqueous phase and stirred for at least 15 min after which the phases separated. The first organic (THF) phase was concentrated to approximately 3.5 rel vols by vacuum distillation at 40 °C. The second organic (DCM) phase was added to the concentrate, the phases were separated, and the organic phase was concentrated to approximately 3.5 rel vol by atmospheric distillation. Di-*iso*-propylether (10 rel vol) was added to the residue from the distillation at 40−45 °C. After concentration to approximately 5 rel vol by vacuum distillation more di-*iso*-propylether (5 rel vol) was added, and the resulting slurry was cooled to ambient temperature and stirred for approximately 60 min. The product was isolated by filtration, washed with di-*iso*-propylether (2 × 1 rel vol), and dried at ambient temperature to give the title compound in approximately 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, J = 9.6, 2.2 Hz, 2H), 3.54 (d, J = 4.9 Hz, 2H), 2.78 (s, 3H), 2.67 (t, J = 12.0 Hz, 2H), 1.70−1.56 (m, 2H), 1.54 (s, lH), 1.36 (qd, J = 12.5, 4.2 Hz, 2H).

Preparation of (1-Methanesulfonylpiperidin-4-y1)methanal (6). A solution of DCM (5 rel vol) and oxalyl chloride (3 mol equiv) was cooled to below− 70 °C. In a separate vessel, DCM (2 rel vol) and DMSO (6 mol equiv) were mixed before addition to the oxalyl chloride solution via a syringe, keeping the temperature below −64 °C during the addition. After stirring for 10 min a solution of (1-methanesulfonylpiperidin 4-yl) methanol (**5**) (l mol equiv) in DCM (5 rel vol) and DMSO (0.5 rel vol) was added, keeping the temperature below −60 °C during the addition. The reaction mixture was held at −70 °C for 40 min before adding triethylamine (7.5 mol equiv) slowly via a syringe. The reaction mixture was allowed to warm to room temperature overnight. HCl (2 M, 5 rel vol) was added while cooling the reaction in an ice–water bath. DCM (5 rel vol) was added before separating the layers and washing the DCM layer with HCl (2 M, 5 rel vol), then sodium bicarbonate solution (saturated, 5 rel vol), and finally brine (5 rel vol). The organic solvent was removed from the organic phase in vacuo to leave a concentrated solution of the title compound in approximately 75% yield. ^{1}H NMR (400 MHz, $CDC1_3$) δ 9.69 (s, lH), 3.68−3.54 (m, 2H), 2.96 (ddd, J = 12.3, 9.7, 2.8 Hz, 2H), 2.78 (s, 3H), 2.43 (dquintet, J = 9.5, 4.7 Hz, lH), 2.10−2.00 (m, 2H), 1.81 (dtd, J = 13.8, 9.8, 3.9 Hz, 2H).

Preparation of *iso*-Propyl Malonic Acid (9). Meldrum's acid (**10**, 1 mol equiv) was charged to a reaction vessel followed by toluene (5 rel vol) and *iso*-propanol (0.59 rel vol). The reaction mixture was heated to between 85 and 90 °C until the reaction was complete. The reaction mixture was then cooled to ambient temperature and transferred to a suitable storage container, washing the vessel with toluene (1 rel vol) and adding this wash to the solution of the title compound.

Preparation of *iso*-Propyl 3-(1-methanesulfonylpiperidin-4-yl)propenoate (3). (1-Methanesulfonylpiperidin-4-yl)methanal (**6**, l mol equiv) was charged to a reaction vessel followed by a line wash of toluene (11 rel vol). Piperidine (0.1 mol equiv) was charged to the vessel followed by a line wash of toluene (0.5 rel vol) and the reaction mixture heated to between 85 and 95 °C. A solution of the *iso*-propyl malonic acid (**9**, 1.25 mol equiv) in toluene (prepared as described above) was added in 10 approximately equal portions over 6−8 h, and the reaction mixture was stirred at between 85 and 95 °C until it reached completion. The reaction mixture was then cooled to between 40 and 50 °C, and HCl (0.5 M, 3 rel vol) was added to the reaction, maintaining the temperature between 40 and 50 °C. After stirring for at least 15 min the phases were separated. Sodium bicarbonate (0.5 M, 3 rel vol) was added to the organic phase, still maintaining the temperature between 40 and 50 °C. The two-phase mixture was stirred for at least 15 min before separating the phases and washing the organic phase with water (3 rel vol). The organic phase was then concentrated to approximately 16 rel vols by vacuum distillation at between 40 and 50 °C. Toluene (3.5 rel vol) was charged, and the solution was clarified at between 40 and 50 °C and then concentrated to approximately 7 rel vol by vacuum distillation. The mixture was then cooled to between 0 and 10 °C and stirred for at least 60 min at this temperature before isolating the title compound by filtration and washing the solid product with toluene (2 rel vol) at between 0 and 10 °C. The solid was dried to give the title compound in approximately 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, J = 15.8, 6.5 Hz, lH), 5.81 (dd, J = 15.8, 0.9 Hz, lH), 5.07 (quintet, J = 6.2 Hz, lH), 3.82 (d, J = 12.0 Hz, 2H), 2.79 (s, 3H), 2.74 (td, J = 12.0, 2.4 Hz, 2H), 2.36−2.17 (m, lH), 1.95−1.80 (m, 2H), 1.57 (ddd, J = 24.9, 11.7, 4.0 Hz, 2H), 1.27 (d, J = 6.4 Hz, 6H).

Preparation of (*R*)-*iso*-Propyl 3-(3,5-difluorophenyl)-3-(1-(methylsulfonyl)piperidine-4-ylpropanoate (17). (*R*)-BINAP (0.0225 mol equiv) and $[Rh(COD)Cl]_2$ (0.01 mol equiv) were charged to a well-inerted reaction vessel. THF (2.8 rel vol) was added, and the mixture was stirred to achieve dissolution (at least 15 min). Meanwhile, *iso*-propyl 3-(1-methanesulfonylpiperidin-4-yl)propenoate (**3**, 1.0 mol equiv),

3,5-difluorophenylboronic acid (1.35 mol equiv), and potassium carbonate (1.35 mol equiv) were charged into a second well-inerted reaction vessel. THF (7.8 rel vol) and *iso*-propanol (1.0 mol equiv) were then added, and the mixture was stirred and heated to 60 °C. The catalyst solution in the first vessel was charged to the second vessel. THF (1.4 rel vol) was charged to the first vessel and then transferred to the main vessel as a line wash. The batch was held at 60 °C until the reaction was complete. Water (2 rel vol) was charged to the reaction at 60 °C. After stirring for at least 15 min, the phases were separated, and the remaining organic phase was washed with brine (2 rel vols) at 60 °C. Oxone (0.09 mol equiv) was charged to the organic layer, and the mixture stirred for 1 h at 60 °C. Water (2 rel vol) was charged, the mixture was stirred, and the phases were then separated to remove the Oxone. Smopex-234 was charged to the reaction vessel, and the contents were stirred for 24 h at 60 °C or until an appropriate reduction in level of rhodium was achieved. The solution was then filtered to remove the Smopex-234, and THF (2 rel vol) was charged to the vessel as a line wash and combined with the product solution. The combined THF phase was then concentrated to 3.5 rel vol. *iso*-Propanol (12 rel vol) was added and further concentration to 3.5 rel vol performed, followed by a final refill of *iso*-propanol (10.5 rel vol). The reaction was then cooled to 30 °C for 30 min in order to precipitate out any remaining low-solubility impurities. After reheating the reaction to between 70 and 75 °C, the impurities were removed by a hot filtration before cooling the reaction to 50 °C. MTBE (1.5 rel vols) was used to wash the solid on the filter before being added to the *iso*-propanol solution of the product. A small sample was removed to provide seed crystals. The solution was then cooled at 12 °C per minute to 20 °C (seed crystals were added at around 40 °C if required). After holding at 20 °C overnight, the title compound was isolated by filtration under suction and washed on the filter with *iso*-propanol (3.5 rel vol). After drying at 50 °C under reduced pressure the product was obtained in 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 (3H, d, $J = 6$), 1.02 (3H, d, $J = 6$), 1.10 (lH, qd, $J = 12.5$ and 4), 1.18 (lH, qd, $J = 12.5$ and 4), 1.33 (lH, d, $J = 12.5$), 1.60 (lH, m), 1.88 (lH, d, $J = 12.5$), 2.49–2.66 (3H, m), 2.80 (lH, dd, $J = 15$ and 5), 2.81 (3H, s), 2.91 (lH, m), 3.46 (lH, d, $J = 12$), 3.57 (lH, d, $J = 12$), 4.71 (lH, septet, $J = 6$), 6.98 (2H, dd, $J = 8$ and 1.5), 7.05 (lH, tt, $J = 9.5$ and 1.5).

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