Organic Process Research & Development **2008,** *12,* 530–536

Ligandless Heck Coupling between a Halogenated Aniline and Acrylonitrile Catalyzed by Pd/C: Development and Optimization of an Industrial-Scale Heck Process for the Production of a Pharmaceutical Intermediate

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Abstract:

The aniline derivative 3 is a key building block of rilpivirine (TMC278) 2, a new potent NNRTI compound under clinical evaluation. In this paper we describe the development of a new synthesis of 3 based on a Heck coupling between a halogenated aniline and acrylonitrile using low loading of Pd/C (0.5 mol %) as catalyst. This resulted in a process which has been successfully transferred into production on 2400 mol-scale (6000 L reactor)

Introduction

Since its discovery in the early 70s by Mizoroki and Heck, the commonly called "Heck reaction" is one of the most powerful tools to create C−C bonds by reacting halogenated aromatics and olefins.[1] In the past decade, new generations of homogeneous catalysts such as palladacycles, pincer-ligands, and more recently bulky electron-rich ligands have extended the scope of the reaction to all aromatic halides, even the poorly reactive aryl chlorides.[2] Nevertheless, from the perspective of process development, homogeneous catalysis suffers from several drawbacks. First, ligands are required to form the active catalyst. These ligands may be expensive, not available in bulk or privileged. Also, the removal of the catalyst (the ligand, the metal or the complex) from the product can be challenging as the residual palladium at the API level has to be consistently under 10 ppm. For these reasons, only few Heck processes are used at production scale in the pharmaceutical industry.[3] In this article, we would like to report the development of a Heck process which has been successfully transferred into production at full-scale (2400 mol/6000 L reactor).

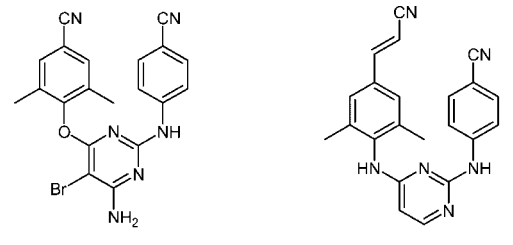
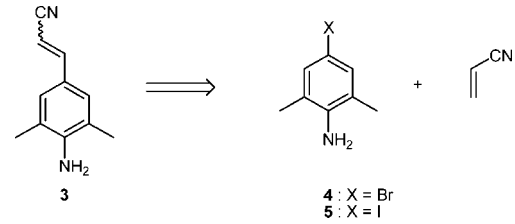


Figure 1. **Structures of etravirine and rilpivirine**

Scheme 1



As part of our HIV program at Johnson & Johnson, two new non-nucleoside reversed transcriptase inhibitors (NNRTIs) are under active development: the recently FDA approved Intelence (etravirine, TMC125) **1** and rilpivirine (TMC278) **2**[4] (Figure 1).

For the commercial synthesis of TMC278, the intermediate **3** was required. This intermediate was first synthesized in a four-step sequence from the commercially available 4-bromo-2,6-dimethylaniline **4**[4b] and our goal became to develop a more efficient and cost-effective synthesis. Therefore we have decided to develop a Heck coupling between the halogenated aniline derivatives **4** or **5** and acrylonitrile that would provide **3** in a single step (Scheme 1).

Results and Discussion

Initial Screening. In order to gain an understanding of the reactivity of our aniline derivatives, the commercially available

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(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (c) Review: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066 and references therein.
(2) (a) Review: Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Review: Whitecombe N. J.; Hii, K.; Gibson, S. *Tetrahedron* **2001**, *57*, 7449−7476. (c) Review oriented towards Process Chemistry: Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553−1582.
(3) (a) Beller, M.; Zapf, A.; Mägerlein, W. *Chem. Eng. Technol.* **2001**, *24*, 575–582. (b) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086–1092. (c) Prashad, M. *Top. Organomet. Chem.* **2004**, *6*, 181–203.
(4) (a) Janssen, P. A. J.; Lewi, P. J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Bethune, M.-P.; Pauwels, R.; Das, K.; Clark, A. D., Jr.; Frenkel, Y. V.; Hughes, S. H.; Medaer, B.; De Knaep, F.; Bohets, H.; De Clerck, F.; Lampo, A.; Williams, P.; Stoffels, P. *J. Med. Chem.* **2005**, *48*, 1901–1909. (b) Medicinal Chemistry synthesis of **3**, unpublished results.

Published on Web 05/16/2008
10.1021/op8000383 CCC: $40.75

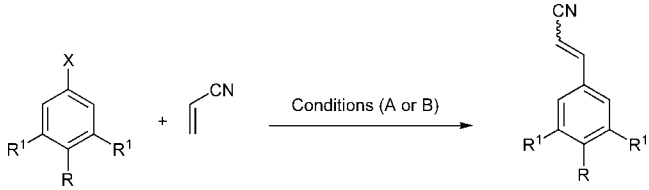
Table 1. **Screening Heck reaction conditions of bromo- and iodo-derivatives with acrylonitrile**

entry	R	R^1	X	cond.	yield ($E + Z$)[a]	E/Z[a]
1a	H	H	Br	A	5.6	74/26
1b				B	72.9	72/28
1c			I	A	92.8	78/22
1d				B	99.0	76/24
2a	NO_2	H	Br	A	100	74/26
2b				B	100	75/25
2c			I	A	91.8	80/20
2d				B	100	75/25
3a	OMe	H	Br	A	4.1	73/27
3b				B	75.2	75/25
3c			I	A	96.8	77/23
3d				B	99.9	75/25
4a	NH_2	H	Br	A	6.5	76/24
4b				B	29.9[b]	76/24
4c			I	A	93.6	78/22
4d				B	99.7	79/21
5a	NH_2	Me	Br	A	3.0	80/20
5b				B	87.5	80/20
5c			I	A	100	79/21
5d				B	94.3	80/20

[a] Yield (%) of products (E+Z isomers) from GLC analysis using an internal standard (diethylene glycol di-*n*-butyl ether). [b] Yield was 40% after 4 h but decreased with time as the Heck product reacts with acrylonitrile to give the corresponding Michael adduct (detected by GLC−MS).

bromo derivative **4** and the easily synthesized iodo derivative **5**[5] were compared as potential starting materials. Both homogeneous and heterogeneous Heck conditions[6] were evaluated (Scheme 2, Table 1).

Scheme 2[a]



[a] A: 10% Pd/C wet (0.05 equiv), DMA, NaOAc, 140°C, 20 h. B: $Pd(OAc)_2$ (0.05 equiv), tri-*o*-tolylphosphine (0.10 equiv), DMA, NaOAc, 140°C, 20 h.

As previously reported in the literature, all the Heck reactions with acrylonitrile afforded a mixture of *E*/*Z*-olefins in ratio ~75/25 to 80/20. The iodides and the activated bromide reacted quantitatively using Pd/C as catalyst (entries 1 to 5/c,d and 2a,b). The nonactivated bromides gave low conversion (3−6.5%) with Pd/C (entries 1,3,4,5/a) but high conversion (75−87%) with the homogeneous system $Pd(OAc)_2$/tri-*o*-tolylphosphine (entries 1,3,4,5/b).

(5) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.

(6) (a) Homogeneous conditions adapted from: Herrmann, W.; Brossmer, C.; Ofele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1847. (b) Heterogeneous conditions adapted from: Köhler, K.; Heidenreich, R.; Krauter, J.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622−631.

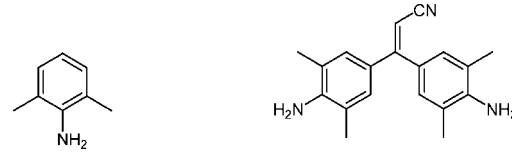
(7) T_r: reaction mixture temperature, T_j: jacket temperature, Q_r: heat of reaction, Q_b: baseline for Q_r. The reaction enthalpy (ΔH_r) is calculated by integration as the area between the Q_r curve and the baseline Q_b ($\Delta H_r = (Q_r - Q_b) \cdot dt$). The thermal conversion ($\alpha(t)$) is calculated from the integral of Q_r and normalized to 100%. Thermal conversion at the time (t) is given by $\alpha(t) = \Delta H_r(t)/\Delta H_r(E)$ x 100 where $\Delta H_r(t)$ = reaction enthalpy from start to time t and $\Delta H_r(E)$ = reaction enthalpy over the entire reaction time (In this case, initial time is dosing start).

Interestingly, results obtained with bromo- and iodo-derivatives **4** and **5** (entries 5a−d) showed that both halides can be used for the synthesis of the desired intermediate **3**. For these two anilines, we have not observed any Michael addition of the aniline with acrylonitrile (compared to entry 4b). Presumably the two flanking methyl groups are sterically impeding this competing reaction.

On the basis of these preliminary results, it was decided to develop processes with **4** and **5** in parallel in order to evaluate which one would be most suitable to be transferred to chemical production.

Conditions for a Heck Reaction with 4-Iodo-2,6-dimethylaniline (5). *Catalyst Loading.* Palladium on charcoal (10% Pd/C, wet) is sufficient to catalyze the reaction, no supplementary ligand or salt being required (Table 1, entry 5c). The reaction is very selective, the main side products **6** (from dehalogenation) and **7** (double Heck product) were each formed in less than 1%, and we have found that it was possible to reach more than 99% conversion by using only 0.1 mol % of catalyst, although we have typically used loadings of 0.5 mol % to ensure robustness (Scheme 3, Table 2).

Scheme 3



6 **7**

Table 2. **Heck reaction of 3 with different catalyst loading (10% Pd/C, wet)**

entry	cat. loading (mol %)	**3**[a]	**5**[a]	Σ rest[b]
1	0.5	96.2	0.4	3.4
2	0.4	94.2	−	5.8
3	0.2	91.5	−	8.5
4	0.1	96.3	0.7	3
5	0.05	84.0	12.9	3.1

[a] Determined by HPLC analysis (area % at 254 nm). [b] Sum of the total remaining impurities determined by HPLC analysis (area % at 254 nm).

Reaction Safety. The initial scale-up of this reaction revealed significant exothermic behavior. When all the compounds were mixed together and the mixture heated to 140 °C, the temperature rose from 110 to 150 °C in one minute. A common way to manage the exothermicity is to operate via a controlled addition of the reagents. RC1 experiment showed that addition of a solution of **5** and acrylonitrile in DMA (over 2 h) onto a warm suspension (140 °C) of Pd/C, NaOAc in DMA effectively controlled the exothermicity and allowed complete conversion after 17 h at 140 °C (Table 3).

Table 3. **Conversion observed during the RC1 experiment (1.2 mol scale)**

time[a] (h)	**3**[b]	**5**[b]	Σ rest[c]
3	76.2	21.8	2.0
6	91.3	5.7	2.8
17	96.2	0.4	3.4

[a] Including dosing time of **5**. [b] Determined by HPLC analysis (area % at 254 nm). [c] Sum of the total remaining impurities determined by HPLC analysis (area % at 254 nm).

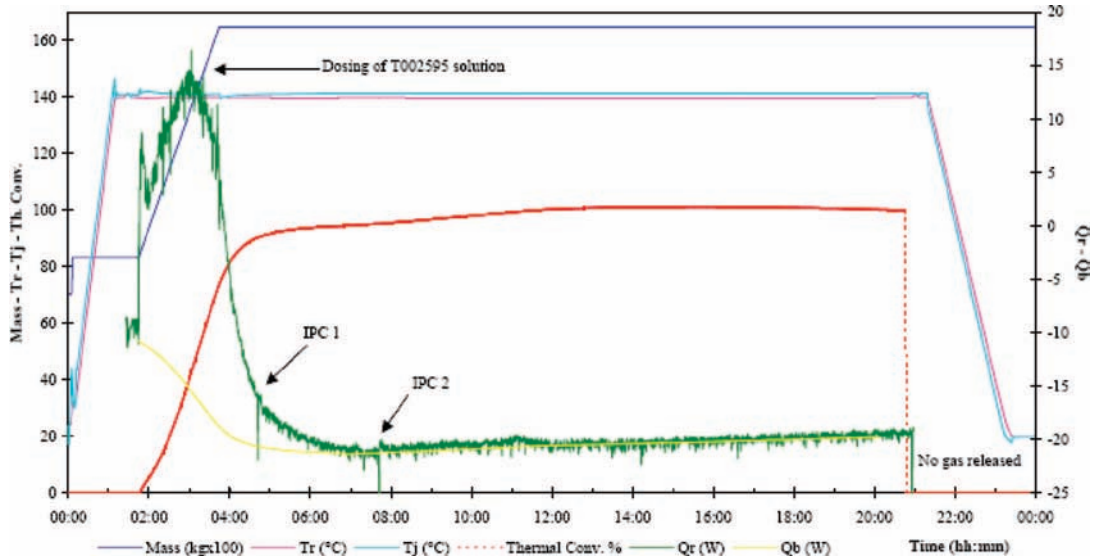


Figure 2. **Temperature profile during the Heck reaction[7] (RC1, 2-L glass reactor, Hastelloy Tr sensor, HC calibration probe, HC large propeller stirrer, and Ritter TG1 gas meter).**

By using this mode of addition, the reaction can be safely performed at Pilot-Plant and Production scale. The reaction shows a medium exotherm (191 kJ/mol), and the accumulation at the end of the dosing is only 26% (Figure 2).

Leaching and Residual Palladium. The amount of residual palladium at the level of intermediates **3** or **8** was assessed as part of our strategy for the control of the palladium content on the final API. We anticipated that the use of a heterogeneous "pre-catalyst" would be advantageous as the reactive palladium nanoparticles[8] would agglomerate back onto the support surface upon completion of the reaction, allowing Pd removal by filtration of the catalyst.[9] This assumption was confirmed by our results (Scheme 4).

The leaching reached ~27% (1340 ppm palladium in solution at 75% conversion) but decreased to only 10% (500 ppm) in the DMA solution after removal of the catalyst by filtration. The level of palladium can be further reduced by a simple treatment of the organic layer with activated charcoal (20 ppm of Pd remained in **3**) which will ensure less than 5 ppm on the isolated product **8**.

Conditions for a Heck Reaction with 4-Bromo-2,6-dimethylaniline (4). *Catalyst Screening.* A ligand screening for the bromoaniline derivative **4** using 5 mol % Pd (Pd/L: 1/2), DMA, NaOAc, 140 °C for 24 h showed that two phosphines, tri-*o*-tolylphosphine and tri-*tert*-butylphosphine, provided more than 90% conversion (Figure 3). We chose these two phosphines for further development.

From the pioneer work of Jeffery on the influence of tetraalkylammonium salts on the Heck-type reaction, it is known that these salts can enhance the reactivity as well as the stability

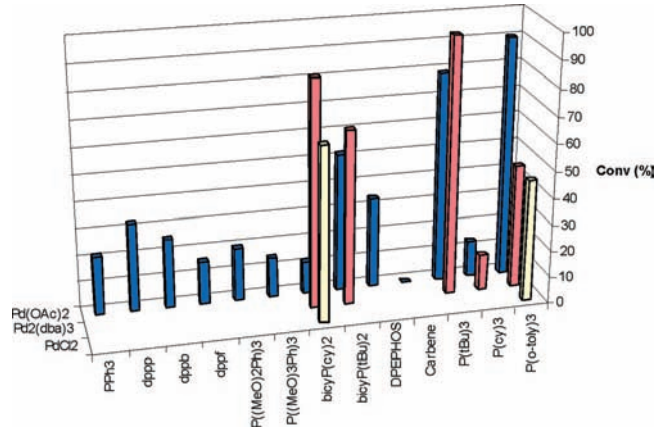
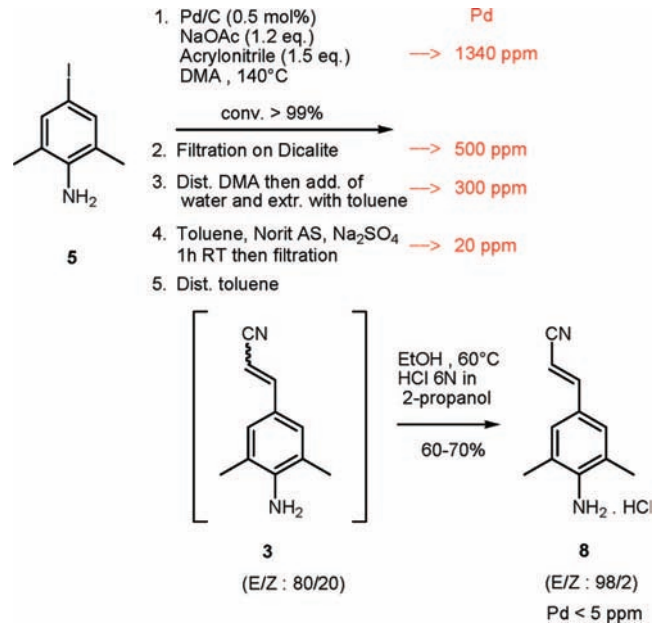


Figure 3. **Ligand screening for the Heck coupling (conversion based on HPLC results - area %).**

Scheme 4



(8) For palladacycles, pincers and several heterogeneous Pd catalysts, the Heck coupling occurs at high temperature (120−160 °C). At these temperatures, they have tendency to form soluble Pd^0 nanoparticles which are the true catalytic species. For more detailed discussion, see de Vries, J. G. *Dalton Trans.* **2006**, 421–429 and references therein.

(9) Review see: (a) Köhler, K.; Pröckl, S.; Kleist, W. *Current Org. Chem.* **2006**, *10*, 1585–1601, Review: (b) Phan, N.; Van Der Sluys, M.; Jones, C. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (c) Thathagar, M.; ten Elshof, J.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2886–2890.

Table 4. **Screening Heck reaction conditions using $Pd(OAc)_2$, P(*o*-tol)$_3$ or P(*t*-Bu)$_3$.HBF$_4$, $Bu_4N^+Cl^-$**

entry	$Pd(OAc)_2$ (mol %)	P(*o*-tol)$_3$ (mol %)	P(*t*-Bu)$_3$·HBF$_4$(mol %)	Bu_4NCl[a] (equiv)	time (h)	conv.[b] (area %)
1	5	10	–	1	24	94.2
2	5	10	–	1.5	24	91.5
3	4	8	–	1	48	99.7
4	3	6	–	1	48	94.9
5	2	4	–	1	48	91.0
6	1	2	–	1	24	77.8
7	1	2	–	0.5	24	67.7
8	5	–	10	1	4	99.2
9	1	–	2	1	48	94.1
10	0.5	–	1	1	48	76.6
11	0.25	–	0.5	1	48	73.2

[a] Tetrabutylammonium chloride used is 95% purity (technical grade). [b] determined by HPLC analysis (area % at 254 nm).

of the catalyst.[10] For the reaction of **4** with acrylonitrile (NaOAc, DMA, 140 °C), it was found that the use of $Bu_4N^+Cl^-$ [11] was beneficial with both phosphines (Table 4).

With one equivalent of $Bu_4N^+Cl^-$, complete conversion was obtained (entries 1,3,8,9) while using 1.5 equiv (entry 2) or 0.5 equiv (entry 7) showed reduced efficiency. Regarding the residual palladium content,[12] we considered the use of a heterogeneous source of palladium in combination with a phosphine ligand. This concept has been extensively investigated by Lipshutz for Ni/C with external phosphine ligands and more recently by Merck researchers for Suzuki coupling with Pd/C[13] Not surprisingly, we obtained similar results in the Heck coupling (Table 5).

Table 5. **Screening Heck reaction conditions using Pd/C (10% Pd/C, wet), P(*o*-tol)$_3$ or P(*t*-Bu)$_3$.HBF$_4$ and $Bu_4N^+Cl^-$**

Entry	Pd/C (mol %)	P(o-tol)$_3$ (mol %)	P(t-Bu)$_3$·HBF$_4$ (mol %)	Bu_4NCl[a] (equiv)	time (h)	conv.[b] (area %)
1	2.5	5	–	1	20	99
2	2.5	5	–	1[c]	4	98
3	2.5	5	–	0.5	24	87[d]
4	2.5	1	–	1	48	86
5	1.25	2.5	–	1	24	96.4
6	0.5	1	–	1	24	9.4
7	5	–	10	1	24	99
8	0.5	–	1	1	24	88

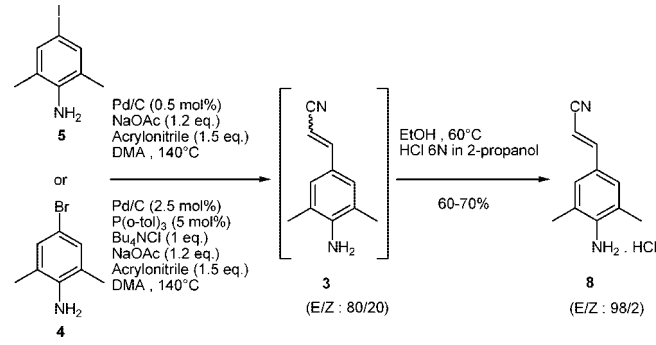
[a] Unless specified, tetrabutylammonium chloride used is 95% purity (technical grade). [b] determined by HPLC analysis (area % at 254 nm). [c] 98% purity tetrabutylammonium chloride (not usable in Plant due to high cost and low bulk availability).The reaction is faster because the technical grade tetrabutylammonium chloride contains up to 5% of tetrabutylammonium which is less reactive and slows down the reaction (see ref 11). [d] 12.5% (area %) double Heck product **7** observed.

On the basis of results of table 4 and 5, and taking into consideration the availability and the cost of the additive and ligand, the following system was chosen for scale-up in the Pilot Plant: Pd/C (2.5 mol %)/P(*o*-tol)$_3$ (5 mol %)/$Bu_4N^+Cl^-$ (1 equiv) in DMA at 140 °C with NaOAc as base.

Reaction Safety. The reaction with **4** is much less exothermic than the reaction with the iodoaniline **5** derivative and can be safely performed in batch mode in the Pilot Plant. This was confirmed by RC1 experiment where complete conversion was obtained after heating the reaction mixture for 20 h at 140 °C.

Heck Processes with Bromo- and Iodo-Derivatives 4 and 5. *Work-Up and Isolation.* Isolation of the reaction product is an important part of a good process. For both reactions (with **4** or **5**), removal of the catalyst by filtration, aqueous workup followed by a salt formation allowed us to isolate the hydrochloride salt **8** in 60−70% yield and high purity (HPLC > 98%) (Scheme 5).

Scheme 5



It is worth noting that during the salt formation, the *E*/*Z* ratio can be increased from 80/20 to 98/2. This is not due to an isomerization but rather to the selective destruction of the *Z*-isomer by Michael reaction with the solvent (Michael adduct is soluble in ethanol) and also to the higher solubility of the *Z*-isomer in ethanol.

Pilot-Plant Campaigns. These processes were implemented in our Pilot Plant, and several campaigns afforded more than 400 kg of **8** (250 kg from **5** and 150 kg from **4**). Nevertheless, an issue in the isolation protocol was identified during the scale-up. In the laboratory filtration proceeded well mainly due to the fact that **8** forms agglomerates. However in the Pilot Plant, pressure filtration was changed to centrifugation, and the agglomerates were broken into very fine particles (8 μm) which obstructed the centrifugation bag, resulting in slower centrifugation and a less efficient washing effect.[14]

For the Heck process using iodo derivative **5**, the residual palladium content was well under control (average 30 ppm with a maximum of 58 ppm). On the other hand, the bromo derivative **4** gave much higher residual Pd content with one case above 1000 ppm (96 to 1196 ppm) necessitating a rework.[15] The extreme value (1196 ppm) is the result of bad centrifugation

(10) Review Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.
(11) Other tetrabutylammonium salts were also tested and the reactivity is the following: $AcO^- \approx F^- > Cl^- > Br^- > HSO_4^- \gg I^-$. Lithium chloride gives 50% conversion while ammonium fluoride gives less than 10% conversion. For economical reasons, we selected the tetrabutylammonium chloride salt (technical grade 95% purity).
(12) First results with homogeneous system (10 mol % Pd used) afforded **8** containing 6600 ppm of residual Pd.
(13) (a) Lipshutz, B.; Blomgren, P. *J. Am. Chem. Soc.* **1999**, *121*, 5819–5820. (b) Lipshutz, B.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem.* **2003**, *68*, 1177–1189. (c) Conlon, D.; Pipik, B.; Ferdinand, S.; LeBlond, C.; Sowa, J.; Izzo, B.; Collins, P.; Ho, G.; Williams, J.; Shi, Y.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931–935.
(14) Interestingly these fine particles (8 μm) were observed only when the salt formation started from an 80/20 *E*/*Z* mixture (**3**). If the salt formation is performed on the pure *E*-isomer (*E* > 98%), much bigger crystals are obtained (average 250 μm), as determined by Lasentec experiments. All our efforts to improve the particle size of **8** starting from the 80/20 *E*/*Z* mixture **3** were unsuccessful.
(15) Rework consisted of neutralization of the hydrochloride salt to liberate the base, extraction of the free base in toluene, treatment of the toluene phase with Silica-thiol followed by a solvent switch to ethanol and salt formation (yield: 80%).

and poor washing effect. So for the bromo derivative **4** significant work would be needed for successful and robust transfer to production.

Selection of the Final Process. Comparison of the two processes is given in Table 6.

Table 6. **Comparison of Heck processes using the bromo-aniline 4 or the iodo-aniline 5**

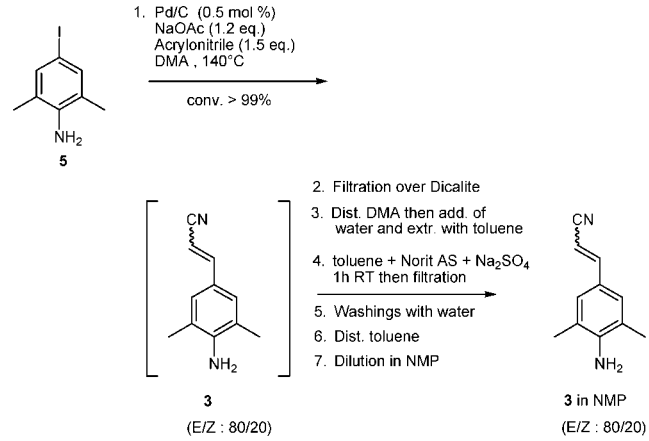
parameter	iodoaniline process	bromoaniline process
yield	same (~65%)	
purity	same (>98%)	
max. residual Pd	**58 ppm**	**1196 ppm**
processability	same	
process Cost	same	
cost of aniline	high	low
cost of catalytic system	low	high
potential for cost decrease	**high**	**low**

Both processes have comparable yield, quality, processability, and cost. However two parameters are in favor of iodoaniline process **5**. First this process was deemed more robust allowing easy and reliable control of the residual palladium content. Second, another advantage of the iodoaniline process is its potential for cost decrease. Although both processes are equivalent in cost, the cost drivers are different. For the iodoaniline process, the major part of the cost is the iodoaniline **5** (80% of the total process cost). For the bromoaniline process, the cheap bromoaniline **4** represents only 20% of the cost, while the catalytic system, which will remain constant, is contributing for more than 70% (higher Pd loading, phosphine ligand, and ammonium salt required). This means that any price decrease of **5** (which is expected with increasing scale) will have a high impact of the total process cost, rendering the iodoaniline process more attractive.[16] Our example illustrates the fact that it is sometimes easier and cheaper to adapt the substrate (choice of iodoaniline **5**) to an inexpensive catalyst (Pd/C) rather than to spend significant resources to find a catalytic system able to perform the same transformation on a cheap and commercially available aryl bromide (or chloride).

For these reasons, the iodoaniline **5** was selected for the final synthesis of rilpivirine.

Final Process Implemented in Chemical Production. In addition to the benefits mentioned above, the iodoaniline **5** afforded pure enough **3** (low Pd level) that we could use in the next step of the synthesis.[17] This allowed us to avoid the difficult isolation of **8** while increasing the overall yield of the reaction to 80%.[18] The final process was first scaled-up in the Pilot then successfully transferred in production at full scale in 6000 L reactors (Scheme 6).

Scheme 6



We were delighted to notice that the exothermicity was completely under control, even when the reaction was performed at full scale in our production facilities. It is also important to mention that no emission of acrylonitrile has been detected during these campaigns.[19] The results of the pilot plant and production campaigns show the robustness and the efficiency of the process. In four production batches more than 1.3 ton of **3** has been produced (Table 7).

Table 7. **Overview of Pilot Plant batches (260 mol) and Chemical Production batches (2388 mol)**

entry	mol-scale	conc.[a]	purity[b]	yield[c]	residual Pd[d]
1	260	21.9	93.7	75.7	56
2	260	21.9	94.6	81.8	40
3	260	21.5	93.0	79.3	28
4	260	21.3	93.4	80.9	35
5	2388	21.1	94.6	82	<5
6	2388	20.9	95.3	81	<5
7	2388	20.5	94.7	80	<5
8	2388	21.3	94.7	82	<5

[a] **3** in the NMP solution (w/w %). [b] HPLC purity (w/w %). [c] Active yield of **3** (%) in the NMP solution. [d] determined by AAS (ppm).

Conclusion

A robust and high-yielding Heck process for the production of **3**, a key intermediate in the synthesis of rilpivirine **2**, has been developed. The use of the more reactive iodoaniline derivative **5** allowed us to perform the reaction without ligand and with low loading of Pd/C as catalyst (0.5 mol %). It is also worth noting that on production scale the reaction can be safely performed by controlled addition of the reagents, that the residual Pd content on **3**, after a simple activated charcoal treatment, is always less than 5 ppm, and that no acrylonitrile emission in the atmosphere has been detected.

(16) As mentioned before in this article, at the beginning of the project, the 4-iodo-2,6-dimethylaniline **5** was not commercially available. After one year, two suppliers were found. Until now, more than seven suppliers have been evaluated. At the time we had to select the process, the price of **5** had already decreased by more than 15 times since our first order. Since then, significant decrease occurred again, confirming our assumption made about the potential of cost decrease. The iodoaniline process (cost for production of **3**) is now 25% cheaper than the bromoaniline process.

(17) The starting *E*/*Z* ratio of the aniline (80/20 for **3** or 98/2 for **8**) is of little importance since a thermodynamic ratio (*E*/*Z*: 85/15) is obtained in the reaction conditions of next step of the synthesis.

(18) The Heck product **3** is an oily residue which solidifies on standing. For ease of handling, and as the next step of the synthesis occurred in NMP, **3** is stored in NMP. This solution is stable over the time (confirmed by suitable stability experiments).

(19) Acrylonitrile is considered as a carcinogenic substance (R 45). The emission in the atmosphere is strictly regulated in Belgium and in Europe (emission <2 mg/m^3 since September 2007).

Experimental Section

Small-scale experiments were carried out using standard glassware, while the experiments on scale were carried out in glass-lined or stainless steel reactors. In the small-scale reactions, the used reagents and solvents were standard technical grade reagents and solvents used without any purification, while Pilot Plant and Production scale experiments were carried out with bulk reagents and solvents. The phosphine ligands used in the screening experiments were purchased from Acros, Aldrich or Strem and used without any purification. The tri-*o*-tolylphosphine was purchased from Rhodia and used without any purification. The palladium on charcoal used in laboratory and production was purchased from Degussa (10% Pd/C, wet) and was used without any purification or treatment. This Pd/C containing in average 50% of water, the quantity of catalyst is calculated on the basis of 10 mol% Pd present on the dry support (i.e.: 1.06 g catalyst contains 5×10^{-4} mol of Pd). The activated charcoal used in laboratory and production (for the removal of residual palladium) was purchased from Norit Americas Inc., type Norit A Supra and was used without any purification or treatment. At the beginning we used the 4-bromo-2,6-dimethylaniline **4** from Acros or Aldrich and 4-iodo-2,6-dimethylaniline **5** synthesized according to literature method.[5] Then bulk **4** and **5** from different suppliers were used in the laboratory and on scale without further purification (HPLC assay >97 w/w %). For analytical purpose, pure **7**, **3** (***E*-isomer**) and **3** (***Z*-isomer**) were synthesized.

HPLC analyses were performed on reversed-phase columns (waters XTerra RP 3.5 μm, 4.6 mm × 50 mm) in gradient mode (ammonium acetate buffer to acetonitrile) with UV detection (254 nm). GLC analysis were performed on Hewlett-Packard 5890 series II (capillary column HP 5, 10 m) in temperature gradient mode (50 to 300 °C, rate 10 °C/min.) with FID detection. High resolution mass were performed on Jeol-JMS-T100LP (DART ionization). NMR spectra were recorded on a Bruker AV 400 and 360 instrument. Palladium determination were performed by AAS on a Varian SpectrAA-880.

The quantitative analytical results (HPLC w/w %, AAS for palladium determination) of Pilot Plant and Production batches were performed by the Chemical Process Control Department according to GLP procedures using validated methods.

Synthesis (1.2 mol-scale) of 3-(4-Amino-3,5-dimethylphenyl)acrylonitrile (3). In a four-necked RBF with mechanical stirrer were placed 118.13 g sodium acetate (1.44 mol, 1.2 equiv), 12.77 g 10% palladium on charcoal, wet (6.00 mmol, 0.005 equiv) and 750 mL dimethylacetamide (DMA). The suspension was heated to 140 °C. At this temperature a solution of 296.49 g of **5** (1.20 mol, 1 equiv), 119 mL acrylonitrile (1.80 mol, 1.5 equiv) and 450 mL DMA was added dropwise to the reaction mixture over 2 h. After 21 h at 140 °C, the reaction mixture was cooled to room temperature. After addition of 6.4 g of filter aid, the reaction mixture was stirred for 1 h at room temperature, and then filtered (paper filter); the filter cake was washed with 60 mL of toluene, and the filtrate was concentrated under reduced pressure (rotavap: 10 mbar/90 °C) to give an oily residue (711 g). To this residue was added 1.2 L of water, 1.2 L of toluene, and 14.8 g of filter aid. The suspension was stirred for 1 h at room temperature and then filtered (paper filter). The filtrate was transferred in a separation funnel, and after decantation, the layers were separated. The water layer was extracted with 600 mL of toluene, and the combined organic layers were washed with 600 mL water in the presence of 14.8 g of filter aid. After filtration (paper filter), the filtrate was transferred in a separation funnel, and after decantation, the layers were separated. The organic layer was washed a second time with 600 mL and then treated with 14.82 g of sodium sulfate anhydrous and 14.82 g Norit A Supra. The suspension was stirred for 2 h at room temperature and then filtered (paper filter) to give the final toluene layer. The toluene layer was concentrated under reduced pressure (rotavap: 10 mbars/ 90 °C). The oily residue obtained was diluted with 600 mL of *N*-methylpyrrolidinone (NMP) to give **3** in NMP

Physical yield: 802.7 g of NMP solution containing **3**.

Active yield: concentration of **3** is 21.3 w/w % → 170.97 g of **3** (0.9927 moles, 82.73%).

***3** (mixture 80/20 of **E/Z-isomers**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, ***Z*-isomer**), 7.22 (d, J = 16.3 Hz, *E*-isomer), 7.05 (s, *E*-isomer), 6.91 (d, J = 12.4 Hz, ***Z*-isomer**), 5.59 (d, J = 16.8 Hz, ***E*-isomer**), 5.11 (d, J = 12.0 Hz, ***Z*-isomer**), 4.04 (br s, ***E*+*Z*-isomers**), 2.21 (s, ***Z*-isomer**), 2.19 (s, ***E*-isomer**).

The *E/Z* ratio was determined by integration of the olefinic protons at δ = 5.59 (d, J = 16.8 Hz, ***E*-isomer**) and 5.11 (d, J = 12.0 Hz, ***Z*-isomer**).

3 (pure ***E*-isomer**) and **3** (pure ***Z*-isomer**) were obtained from the 80/20 *E/Z* mixture after separation by preparative HPLC (preparative Chiralcel OJ column, 100% ethanol).

***3** (pure **E-isomer**):* ^{1}H NMR (360 MHz, $CdCl_3$): δ = 7.21 (d, J = 16.4 Hz, 1H), 7.04 (s, 2H), 5.58 (d, J = 16.5 Hz, 1H), 3.96 (br s, 2H), 2.18 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 150.9, 146.2, 128.0, 123.3, 121.5, 119.6, 90.2, 17.5. High resolution mass confirms the elemental composition.

***3** (pure **Z-isomer**):* ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.46 (s, 2H), 6.89 (d, J = 12.5 Hz, 1H), 5.10 (d, J = 12.1 Hz, 1H), 3.98 (br s, 2H), 2.19 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 148.7, 145.9, 129.8, 123.6, 121.2, 118.8, 88.7, 17.5. High resolution mass spectrometry confirms the elemental composition.

Industrial synthesis (2388 mol) of 3-(4-amino-3,5-dimethylphenyl)acrylonitrile (3). A 6000 L glass-lined reactor (reactor 1) was inertised with nitrogen then charged with 25.5 kg (12 mol, 0.005 equiv) of 10% Pd/C (wet) and 1400 kg DMA. The suspension was stirred and 235 kg sodium acetate (2865 mol, 1.2 equiv) were added. The suspension was heated to 140 °C (range ± 5 °C).

A 6000 L stainless steel reactor (reactor 2) was inertised with nitrogen then charged with 190 kg (3581 mol, 1.5 equiv) of acrylonitrile, 700 kg DMA and 590 kg (2388 mol, 1 equiv) 4-iodo-2,6-dimethylaniline **5**. The solution was stirred for 1 h 30 min at room temperature. This solution was transferred via a 500 L glass addition flask onto the warm suspension in reactor 1 over 2 h (T_{min} 137 °C, T_{max} 140 °C). Reactor 2 was rinsed with 150 kg of DMA also transferred into reactor 1. After the addition, the suspension in the reactor 1 was stirred at 140 °C for 17 h, then cooled to room temperature: IPC check for complete conversion was performed before the workup (<1% **5** by HPLC); 11.9 kg of filter aid was added, and the reaction

mixture was stirred for 30 min and then filtered through filter plates (three filters in parallel). The filtrate was transferred to reactor 2 (which was first cleaned using toluene). Reactor 1 was rinsed three times with 200 L of toluene, also transferred to reactor 2 via each plate filter used. (Reactor 1 was washed with water for the removal of the residual palladium on charcoal from the wall). In reactor 2, the reaction mixture was concentrated by vacuum distillation of the solvents (industrial vacuum, reactor temperature 142 °C). The residue was cooled to 100 °C, and then 2400 L of toluene was added, followed by addition of 2400 L of water and 29.2 kg of filter aid. The solution was stirred vigorously for 30 min and transferred into reactor 1 via a mobile plate filter. In reactor 1, the layers were separated after decantation. The water layer was transferred in reactor 2 (while the organic layer stayed in reactor 1), washed with 2400 L of toluene, and then discarded. The organic layers were combined in the reactor 2. To the combined organic layers were added 1200 L water and 28.6 kg filter aid. The mixture was stirred vigorously for 30 min and transferred into reactor 1 via a mobile plate filter. After decantation, the layers were separated, and the water layer was discarded; 1200 L of water was added, and the mixture was stirred vigorously for 30 min. After decantation, the layers were separated, and the water layer was discarded. The resulting organic layer was treated with 28.6 kg of sodium sulfate and 28.6 kg of Norit A Supra. After 2 h 30 min stirring at room temperature it was transferred into reactor 2 (previously cleaned with water) via a mobile plate filter: IPC before removal of the toluene (<50 ppm Pd by AAS). Toluene was removed by vacuum distillation (industrial vacuum, reactor temperature 94 °C), and the warm residue of **3** was diluted with 1225 kg of *N*-methylpyrrolidone (NMP). The NMP solution of **3** was cooled to room temperature and transferred in metallic drums of 200L.

Physical yield: 1591 kg of in NMP solution containing **3**.

Active yield: concentration of **3** is 20.9 w/w % → 332.5 kg of **3** (1931 mol, 81%).

Residual Pd content: <5 ppm

Synthesis of 3,3-Bis(4-amino-3,5-dimethylphenyl) acrylonitrile 7.[20] In a 100 mL RBF with magnetic stirrer were placed 1.7 g of **3** (0.01 mol, 1 equiv), 4.9 g of **5** (0.02 mol, 2 equiv), 112.3 mg of palladium acetate (0.0005 mol, 0.05 equiv), 3.5 g of tetra-*n*-butylammonium bromide (0.011 mol, 1.1 equiv) and 30 mL of DMA. The reaction mixture was heated at 80 °C for 44 h (at this moment the conversion is ca. 85%, determined by GLC, area %) then allowed to cool down to room temperature. The reaction mixture was filtered through a Dicalite pad. The filtrate was transferred in a separation funnel and partitioned with 150 mL of water and 100 mL of toluene. After phase separation, the obtained organic layer was treated with Norit A Supra, filtered, and concentrated under vacuum to give 5 g of a dark brown oily residue. **7** (0.9 g, 0.0031 mol, 30.9% yield, GC purity >99%) was obtained by crystallization from ethyl acetate/hexane (1/2).

7: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.05 (s, 2H), 6.92 (s, 2H), 5.36 (s, 1H), 3.84 (br s, 4H), 2.18 (s, 6H), 2.14 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 163.9, 145.1, 144.5, 130.1, 129.1, 126.9, 121.1, 121.0, 119.9, 88.3, 17.6. High resolution mass spectrometry confirms the elemental composition.

Synthesis (0.3 mol-scale) of (2*E*)-3-(4-Amino-3,5-dimethylphenyl)acrylonitrile Hydrochloride (8). The crude oily residue **3** obtained after standard workup and concentration of the toluene layer (rotavap: 10 mbars/ 90 °C) was transferred in a 1 L RBF with mechanical stirrer. To this residue was added 450 mL of ethanol (denaturated with 2% methanol). The solution was heated at 60 °C, and 55 mL of a solution of HCl in isopropanol (6 N, 1.1 equiv) was added dropwise over 1 h (*T* range: 60 °C ± 5 °C). After addition of 10 mL of the HCl solution, seeding material **8** was added (crystallization occurred after addition of 25 mL of HCl solution). After complete addition, the reaction mixture (heterogeneous) was stirred for 1 h at 60 °C and then allowed to reach spontaneously 25 °C. The reaction mixture was filtered (paper filter), and the pale yellow solid was washed with 50 mL of isopropanol. The solid was dried at 50 °C under reduced for 16 h to afford 40.4 g of **8** (64.5% yield).

HPLC purity: 98% (w/w). *E*/*Z* ratio: 98/2

8: ^{1}H NMR (360 MHz, DMSO-d_6): δ = 9.12 (br s, 3H), 7.48 (d, J = 16.5 Hz, 1H), 7.35 (s, 2H), 6.30 (d, J = 16.5 Hz, 1H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ =150.6, 143.6, 128.1, 124.3, 123.6, 119.7, 90.8, 17.7.

Based on these results, this Heck reaction will become the industrial process for the production of **3**.

Acknowledgment

We thank Luc Vrins for the preparative separation of the *E*- and *Z*-isomers of **3**, Paul Moons for the determination of residual Pd and Ludwig Goetelen for the HRMS analyses.

Received for review February 21, 2008.

OP8000383

(20) Conditions adapted from Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Pleixats, R.; Roglans, A. *Synthesis* **2002**, 1903–1911.