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Technical Notes

Optimization and Scale-Up of a Suzuki−Miyaura Coupling Reaction: Development of an Efficient Palladium Removal Technique

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Abstract:

A ligand−solvent−base screen was performed on a Suzuki−Miyaura coupling reaction, and the screening data, followed by a set of focused experiments, helped to optimize reaction conditions. Further work was carried out that centered on reducing the level of residual palladium in the isolated product. Treatment of the reaction mixture with toluene and 20% aqueous $NaHSO_3$ at elevated temperature lowered the palladium content from ~8000 ppm to 100 ppm or less. The Suzuki−Miyaura coupling and palladium removal process were demonstrated on 20-L scale, are highly efficient and cost-effective, and require short cycle times.

Introduction

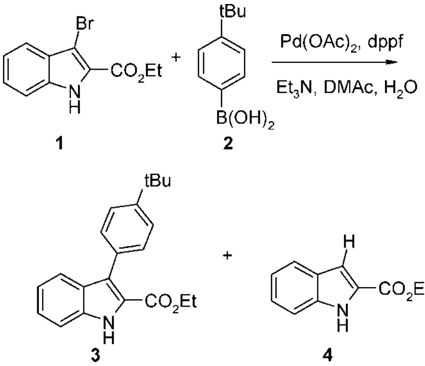
As part of an ongoing drug discovery program in our laboratories, ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1*H*-indole-2-carboxylate **3** was identified as a key synthetic intermediate. In order to support development efforts, we needed to quickly identify high-yielding and reproducible Suzuki−Miyaura coupling reaction conditions with short cycle times to generate **3** on 20-L scale. Additionally, workup conditions needed to be developed that allowed crystallization of **3** from the reaction mixture in high purity with palladium levels <150 ppm. Herein, we report the development of Suzuki−Miyaura coupling conditions optimized for our process; and an efficient, economic method of palladium removal following the coupling reaction.

Results and Discussion

Initial experiments indicated that the Suzuki−Miyaura coupling of commercially available **1** and **2** was an ideal method to generate **3** (Scheme 1).

However, the original reaction conditions developed for the system, $Pd(OAc)_2$, 1,1′-bis(diphenylphosphino)ferrocene (dppf), Et_3N, DMAc, and water, while successful on 50-L scale, had significant drawbacks which included a modest yield (60−66%), generation of variable amounts of reduced indole byproduct (**4**, 0.7−3.6%), and high levels of residual palladium (>2500 ppm) and iron (>250 ppm) in isolated **3**.

Scheme 1. **Suzuki−Miyaura coupling. original reaction conditions**



Therefore, a D-Optimal DoE[1] study that considered three factors, ligand, solvent, and base, was devised to define the reaction conditions. Monodentate, large and small bite angle bidentate, electronically neutral, and electronically rich ligands were incorporated as well as inorganic and organic bases. The inclusion of water in the screen was also a consideration since its presence could have an effect on catalytic turnover.[2] Finally, a variety of solvents likely to work well in Suzuki−Miyaura couplings were selected.[3] The original reaction conditions were included in the screen as a control.

Analysis of the data was represented in a Spotfire plot[4] (Figure 1), and three hits were immediately identified as superior to the control conditions; dppf, DMAc, $KHCO_3$; 1,4-bis(diphenylphosphino)butane (dppb), *n*-butanol, *t*-$BuNH_2$; and P(*o*-tol)$_3$, *n*-butanol, Et_3N.

In addition, the DoE coefficient plot[5] (Figure 2) revealed that the main effects favoring formation of **3** were the solvents

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(1) The experimental design and data analysis were performed using the commercially available program *Modde*, version 6.0; Umetrics, Inc.: Kinnelon, NJ. http://www.umetrics.com/. All screening was performed in HPLC vial microreactors using the iChemExplorer system. http://www.ichemexplorer.com.

(2) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *21*, 2177.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (d) Note: consideration was also given to solvent selection based upon principal component analysis (PCA) diversity and boiling point of the solvent.

(4) Spotfire decision suite available from TIBCO Software, Sommerville, MA. http://spotfire.tibco.com/decision-support-software.html. For a discussion on the use of Spotfire in data visualization and mining, see Higginson, P. D.; Sach, N. W. *Org. Process Res. Dev.* **2004**, *8*, 1009.

10.1021/op800064y CCC: $40.75

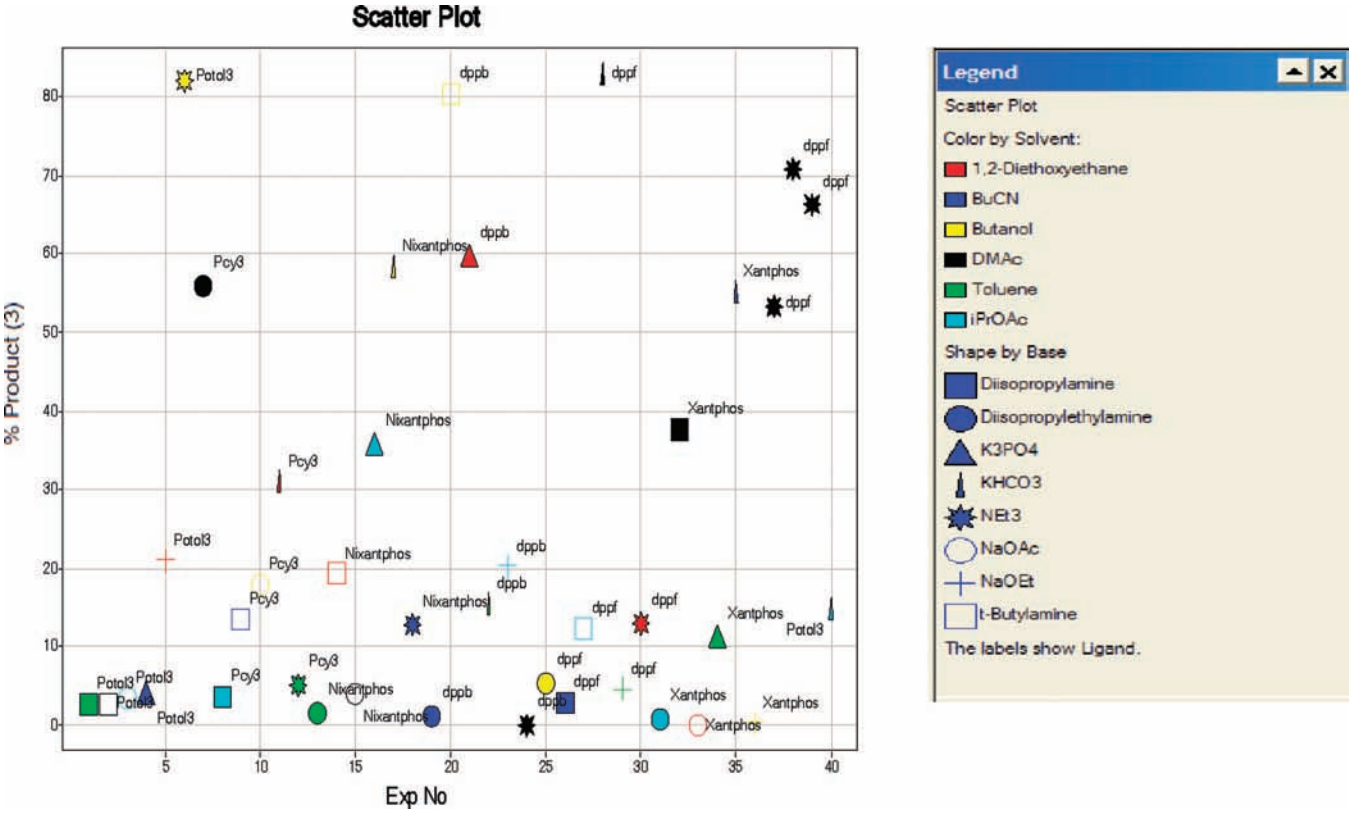

Figure 1. **Output of ligand−solvent−base screen.**

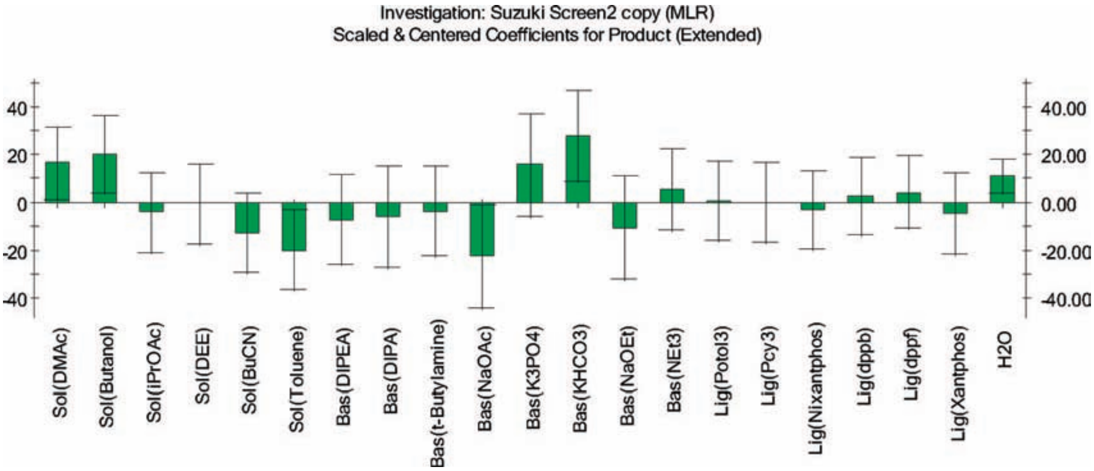

Figure 2. **DOE coefficient plot. Statistically significant factors: DMAc, *n*-butanol, $KHCO_3$, water.**

DMAc or *n*-butanol, the use of $KHCO_3$ as base, and the presence of water in the reaction mixture.

Based on the information gained from analysis of the screen data, four additional experiments were performed, and results are summarized in Table 1.

Faster reaction rates were seen using $KHCO_3$ (entries 1 and 3) and the combination of $KHCO_3$ and $P(o\text{-tol})_3$ was superior, with fastest conversion and minimal undesired reduced byproduct (entry 3).

On the basis of the results of the focused reaction data set, optimal reaction conditions were determined to be $P(o\text{-tol})_3$, $KHCO_3$, *n*-BuOH, and these conditions were successfully performed on multigram scale. Further development work identified the optimal reaction temperature as 60 °C, with complete conversion in <3 h.

Table 1. **Results of Focused Screen**

			$t = 1$ h (area %)	
entry	ligand	base	**3**	**4**
1	dppb	$KHCO_3$	85.1	6.1
2	dppb	t-$BuNH_2$	69.0	6.5
3	$P(o\text{-tol})_3$	$KHCO_3$	94.4	1.25
4	$P(o\text{-tol})_3$	t-$BuNH_2$	61.9	6.9

With reproducible reaction conditions that generate minimal reduced byproduct in hand, we focused our efforts on evaluating workup conditions to maximize the yield and generate **3** with palladium levels <150 ppm. Because this chemistry was ultimately to be performed on kilogram scale, we wanted the

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(5) Plot generated by the application of a regression equation fit to the DoE data. The coefficients of the regression model are plotted to identify the statistically significant factors.

Table 2. **Absorption of Palladium by Solid Phase Treatments**

entry	treatment	palladium in isolated **3** (ppm)
1	none	8058
2	Smopex-110	5092
3	activated carbon	2138
4	phosphotungstic acid-modified alumina	7435
5	phosphotungstic acid-modified carbon	1759
6	ethylene diamine-modified silica	1975
7	mercaptopropyl-modified silica	7266
8	triamine-derived silica	285

workup to be cost-effective and require minimal unit operations with short cycle times.

Initial workup conditions focused on precipitation of the product from the reaction mixture by the addition of water. This resulted in a good yield (~90%); however, palladium levels in **3** were in the range of 12,000 ppm. An alternate workup was examined that utilized methyl *tert*-butyl ether (MTBE), water washes, and crystallization of the product with heptane; however, the yield was only 40−60%. We found that substituting *i*-PrOH as the reaction solvent had no deleterious effect on reaction performance and much higher recoveries could be obtained using the MTBE workup (87%); however palladium levels in **3** were 8000 ppm. Nevertheless, the use of MTBE as a workup solvent gave us a good starting point to screen palladium removal methods.

Numerous methods have been reported in the literature for the removal of residual palladium from organic reaction mixtures, and several papers summarizing methods have been published.[6] We first examined methods of adsorbing or complexing the palladium to a solid scaffold and screened several commercially available palladium scavengers that have been described in the literature.[6a,7] The reaction mixture, after an initial filtration to remove precipitate generated during the reaction, and prior to crystallization of **3**, was subjected to the scavengers, and the palladium levels in isolated **3** were measured (Table 2).

Surprisingly, the screen produced only one hit that was near our target palladium level. While the triamine-derived silica treatment was promising (entry 8), the workup required two filtration steps (pre- and post-scavenger) and long cycle times. Additionally, the cost of the scavenger is relatively high; therefore, we continued investigations into alternate methods and next turned our attention to extraction/precipitation techniques.

Table 3. **Removal of Palladium by Extraction−Precipitation Treatment**

entry	treatment	temp (°C)	time	extraction solvent	palladium in isolated **3** (ppm)
1	15% TMT wash	45	30 min	MTBE	3542
2	10% $NaHSO_3$ wash	45	2 h	MTBE	5134
3	20% $NaHSO_3$ wash	60	1 h	MTBE	193
4	20% $NaHSO_3$ wash	45	30 min	toluene	321
5	20% $NaHSO_3$ wash	60	1 h	toluene	36

We first examined trimercaptotriazine (TMT)[8] and sodium bisulfite. Upon completion of the Suzuki−Miyaura coupling reaction, the reaction mixture was diluted with MTBE or toluene, the wash solution (TMT or $NaHSO_3$) was added, and the slurry was heated. The precipitate was removed by filtration, and product **3** was isolated via crystallization (Table 3).

Initial results were not promising (entries 1 and 2); however, increasing the $NaHSO_3$ concentration and the wash temperature significantly lowered the palladium levels in the product (entry 3). The increase in the wash temperature also ensured that **3** remained in solution during the filtration step.

Moreover, it was found that the crystallization of **3** could be carried out in higher yield using a toluene−heptane solvent system in place of MTBE−heptane. We replaced MTBE with toluene to obviate the need for a solvent exchange, and this change had the added benefit of further lowering palladium levels. With toluene at 45 °C, levels were dramatically lowered compared to the 45 °C MTBE results (entry 4 vs entry 2). Additionally, the effect of the number of washes on palladium levels was also examined with toluene at 45 °C, and results showed that there was no change in residual palladium after one versus three washes. Optimal conditions were achieved with toluene as the extraction solvent, increasing the wash temperature to 60 °C, and extending the wash time to one hour.

We now had both the reaction conditions and workup method defined on small scale, and we next evaluated their performance upon scale-up. The conditions were carried out several times on 1-L scale with 82−86% yield, >98.5% purity (<0.25% of **4**) and palladium levels of 35−45 ppm. Upon scale-up in 20-L equipment an 82% yield of **3** was obtained with >99.8% purity (<0.1% of **4**) and 100 ppm palladium. The workup produced a higher palladium level on 20-L scale than had been observed previously; however, the level was well within our 150 ppm limit.

Both the optimized reaction conditions and the toluene−$NaHSO_3$ wash met our goal of a reproducible process that generated isolated product with <150 ppm palladium. Minimal unit operations, cost effectiveness, and short cycle times were built into the process. Moreover, this palladium removal technique is applicable to other Suzuki−Miyaura coupling reactions and has been utilized to effectively reduce palladium levels in intermediates used in the synthesis of other APIs.

Conclusions

The ligand−solvent−base screen helped to define Suzuki−Miyaura reaction conditions. Our efforts to remove residual palladium from synthetic intermediate **3** identified the removal of palladium from the reaction mixture using a toluene

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(6) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Königsberger, K.; Chen, G-P.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Repiè, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733. (c) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198.

(7) Metals scavenging kit available from Strem chemicals. http://www.strem.com.

(8) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311.

extraction–$\mathrm{NaHSO_3}$ wash system as the most effective method, and both the optimized reaction conditions and palladium removal technique were demonstrated successfully on 20-L scale in 82% yield (>99.8% purity) and 100 ppm palladium.

Experimental Section

Preparation of Ethyl 3-[4-(1,1-Dimethylethyl)phenyl]-1*H*-indole-2-carboxylate (3).[9] *Original, Unoptimized Suzuki–Miyaura Coupling.* Charge the reaction vessel with **1** (2.94 kg, 1.0 equiv), **2** (2.34 g, 1.2 equiv), dppf (0.30 g, 0.05 equiv), $\mathrm{Pd(OAc)_2}$ (0.12 g, 0.05 equiv), $\mathrm{H_2O}$ (2.9 L, 1 vol), and DMAc (17.6 L, 6 vol). Add $\mathrm{Et_3N}$ (6.1 L, 4.0 equiv) and heat at 85 °C for 2–3 h. Cool to 40 °C, add MeCN (2.94 L, 1 vol), and filter off the solids, washing the cake with MeCN (7.35 L, 2.5 vol). Heat the filtrate to 50 °C and add 50% EtOH in $\mathrm{H_2O}$ (17.6 L, 6 vol), maintaining a reaction temperature of 50 °C. Cool the suspension to 0 °C and hold overnight. Filter off the solids, wash the cake with heptane (7.35 L, 2.5 vol), and dry under vacuum to give 2.36 kg (66% yield) of **3** (0.68% of **4**,[10] residual Pd: 3675 ppm, residual Fe: 471).

Ligand–Solvent–Base Screen, General Experimental Procedure. Combine **1** (1.0 equiv,), **2** (1.2 equiv), base (2.0 equiv), ligand (0.1 equiv with respect to number of phosphines), $\mathrm{Pd(OAc)_2}$ (0.05 equiv), solvent (6–7 vol) and water (1 vol, if required). Heat at 85 °C and follow by HPLC for 6 h.

Focused Screen, General Experimental Procedure. Combine **1** (1.0 equiv,), **2** (1.2 equiv), base (2.0 equiv), ligand (0.1 equiv), $\mathrm{Pd(OAc)_2}$ (0.05 equiv), *n*-BuOH (6 vol) and water (1 vol). Heat at 85 °C and follow by HPLC.

Palladium Removal Using Solid-Phase Treatments, General Experimental Procedure. Charge **1**(1.0 equiv), **2** (1.2 equiv), $\mathrm{KHCO_3}$ (2.0 equiv), $\mathrm{P(}o\text{-}\mathrm{tol)_3}$ (0.1 equiv), $\mathrm{Pd(OAc)_2}$ (0.05 equiv), $\mathrm{H_2O}$ (1 vol), and *i*-PrOH (4 vol) and heat at 60 °C for 2 h. Charge MTBE (6 vol) and water (6 vol) and stir the suspension at 45 °C for ~30 min. Filter the mixture, separate the layers, and add the appropriate scavenger (17 wt %) to the organic layer. Stir at 45 °C overnight, filter off the solids, concentrate the organic layer, add heptane, and filter off **3**.

Optimized Suzuki–Miyaura Coupling Used in Scale-Up Runs. Charge the reaction vessel with **1** (1 kg, 1.0 equiv), **2** (800 g, 1.2 equiv), $\mathrm{KHCO_3}$ (750 g, 2.0 equiv), $\mathrm{P(}o\text{-}\mathrm{tol)_3}$ (110 g, 0.1 equiv), $\mathrm{Pd(OAc)_2}$ (40 g, 0.05 equiv), $\mathrm{H_2O}$ (1 L, 1 vol), and *i*-PrOH (4 L, 4 vol) and heat at 60 °C for 2 h under nitrogen.[11] Charge the toluene (6 L, 6 vol) and 20% $\mathrm{NaHSO_3}$ (6 L, 6 vol) and stir the suspension at 60 °C for 1 h. Filter the warm reaction mixture and separate the layers. Concentrate the organic layer to 3 vol under vacuum, add heptane (5 L, 5 vol), cool to 0 °C, and stir overnight. Filter off the solids, wash the cake with heptane, and dry under vacuum to give 983 g (82% yield) of **3** (<0.1% of **4**, residual Pd: 100 ppm).

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[9] Stolle, A.; Dumas, J. P.; Carley, W.; Coish, P. D. G.; Magnuson, S. R.; Wang, Y.; Nagarathnam, D.; Lowe, D. B.; Su, N.; Bullock W. H.; Campbell, A.-M.; Qi, N.; Baryza, J. L.; Cook, J. H. Preparation of substituted indoles as PPAR-γ binding agents. PCT Int. Appl. WO 2002030895 A1 20020418, CAN 136:309846, 2002.

[10] Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4*, 2317.

[11] Small-scale experiments demonstrated the reaction could be successfully run open to the atmosphere. For safety reasons, a nitrogen sweep was used on scale-up.