Organic Process Research & Development **2009**, *13*, 1419–1425

The Discovery and Development of a Safe, Practical Synthesis of ABT-869

Albert W. Kruger,* Michael J. Rozema, Alexander Chu-Kung, Jorge Gandarilla, Anthony R. Haight, Brian J. Kotecki, Steven M. Richter, Albert M. Schwartz, and Zhe Wang

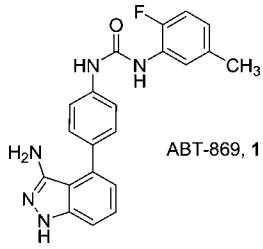
Abbott, Process Research and Development, 1401 Sheridan Road, North Chicago, Illinois 60064-6285, U.S.A.

Abstract:

The discovery, development and implementation of two chemical routes to ABT-869 is reported. Optimization of the first-generation heterocycle formation and Suzuki coupling is briefly described. Key features of the second-generation synthesis include the development of a safe hydrazine condensation by utilizing an inorganic base to increase the onset temperature of exothermic decomposition. The second-generation Suzuki reaction is discussed in detail, culminating in the use of an oxygen monitor as a PAT to maximize reproducibility on scale.

Introduction

Cancerous tissue requires the process known as angiogenesis to maintain a constant supply of blood for a new or growing tumor. As a consequence, interfering with angiogenesis has become a very important area of cancer research.[1] One possible method to interfere with angiogenesis is to interrupt the tyrosine kinase mediated signaling using a small molecule agent. ABT-869 **1** is a potent tyrosine kinase receptor inhibitor under development for the possible treatment of cancer.[2]



ABT-869, **1**

Results and Discussion

First-Generation Route to 1.[3] The first-generation synthesis of ABT-869 commenced with the preparation of aminoindazole **3** from commercially available 2-fluoro-6-iodo-benzonitrile **2** by using 5 equiv of hydrazine monohydrate in refluxing ethanol in the presence of $NaHCO_3$. When less hydrazine was used (3 equiv), the reaction stalled with only partial consumption of **2**. The presence of $NaHCO_3$ was not necessary for conversion of **2** to **3**, but the level of glass etching was reduced with inorganic base present.[4] In general, sodium bases performed better than potassium bases at minimizing glass erosion. The product **3** could be directly isolated from the reaction mixture by subsequent slow addition of water to the reaction mixture. This process led to a 94% isolated yield of **3** (>99% purity).

In an effort to avoid glass vessels, a safety analysis/corrosion study was done that revealed that the reaction mixture was compatible with stainless steel reaction vessels (no metal leaching was detected, nor lower decomposition temperature).[5] However, due to the possibility of surface metal oxide contamination on the surface, stainless steel vessels were not pursued.[6]

The coupling substrate **6** was obtained by condensation of amino-boronate **4** and isocyanate **5**. The reaction proceeded to >95% conversion in toluene at 25 °C over 12 h, but was done in <2 h by warming to 50 °C with no loss of yield or purity. Urea **6**, was isolated by filtration after cooling of the reaction mixture to obtain a 95% yield or could be telescoped directly into the next step. If **6** is used directly in the Suzuki reaction, it is important to quench any excess isocyanate with ethanol before the Suzuki coupling with the heterocycle **3**. Failure to quench resulted in the impurities arising from the reaction of isocyanate **5** with **3**.

First-Generation Suzuki Reaction. Iodide **3** and boronate **6** could be coupled under various conditions to afford crude ABT-869 **1.** Early preparations used the $Pd(dba)_2/PPh_3$ catalyst system (Table 1, entry 1). This catalyst was effective on small scale, but the reaction tended to stall as the reaction was scaled to >50 g. This tendency to stall led to extended reaction times at 75 °C, which in turn led to extensive degradation of **1**. To obtain acceptably pure material chromatographic purification was required to remove the degradation products.

A brief catalyst screen (Table 1, entries 2−4), identified $Pd(dppf)Cl_2$ as having the highest intrinsic reaction rate, as judged by conversion at 2 h. This catalyst system is also resistant to oxygen contamination, achieving >80% conversion in an experiment that was degassed with nitrogen and then left open to the atmosphere (entry 8). However, in the absence of any degassing protocol, the reaction stalled at 22% conversion after

* Author for correspondence.

(1) Ferrara, N.; Kerbel, R. S. *Nature* **2005**, *438*, 967–974. Carmeliet, P.; Jain, R. K *Nature* **2000**, *407*, 249–257.

(2) Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Harris, C. M.; Hickman, D.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Martin, R. L.; Olson, A. M.; Osterling, D. J.; Pease, L. J.; Soni, N. B.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Reuter, D. R.; Davidsen, S. K.; Michaelides, M. R. *J. Med. Chem.* **2007**, *50*, 1584–1597.

(3) The first-generation route is similar to the route that emerged from Medicinal Chemistry.[2]

(4) Testing found that the reaction mixture consumed glass at a rate of 0.54 cm/year. In the presence of $NaHCO_3$ the rate of glass erosion was 0.0 cm/year, but small amounts of etching still occurred by visual inspection.

(5) Metal oxides can catalyze the exothermic decomposition of hydrazine derivatives, see: Speight, J. G., Ed. Lange's Handbook of Chemistry; McGraw-Hill: New York, 2005.

(6) For a general discussion on the safe use of hydrazine, see: Kuethe, J. T.; Childers, K. G.; Peng, Z.; Journet, M.; Humphrey, G. R.; Vickery, T.; Bachert, D.; Lam, T. T. *Org. Process Res. Dev.* **2009**, *13*, 576–580. Hansen, K. B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivera, N.; Steinhuebel, D.; Armstrong, J. D.; Askin, D.; Grabowski, E. J. J. *Org. Process Res. Dev.* **2005**, *9*, 634–639.

10.1021/op900208y CCC: $40.75
Published on Web 10/28/2009

Table 1. **Suzuki coupling of 3 and 6[a]**

entry	catalyst	mol % catalyst	conversion of **3** (time)
1	$Pd(dba)_2/PPh_3$ (1:4 molar ratio)	3	89% (21 h)[d]
2	$Pd_2(dba)_3/PPh_3$	3	78% (2 h)
3	$Pd(PPh_3)_2Cl_2$	3	43% (2 h)
4	$Pd(dppf)Cl_2$	3	>99% (2 h)
5	$Pd(dppf)Cl_2$	1	>99% (2 h)
6	$Pd(dppf)Cl_2$	0.5	78% (2 h)
7	$Pd(dppf)Cl_2$	0.1	22% (2 h)
8	$Pd(dppf)Cl_2$	1	81% (19 h)[c]
9	$Pd(dppf)Cl_2$	1	22% (19 h)[b]
10	$Pd(dppf)Cl_2$	1.1	100% (7 h)[e]

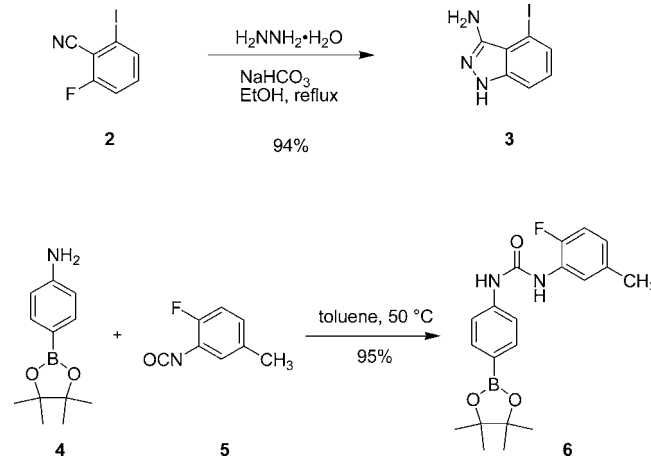
[a] All entries use Na_2CO_3 (2.5 equiv), toluene/ethanol/water (1:1:1) as solvent and reflux (~73 °C). [b] Reaction set up and conducted under air atmosphere. [c] Reaction mixture degassed, then left open to air. [d] Yield by assay (HPLC) was 73%, crude purity was 95.3%. [e] Yield by assay (HPLC) was 96%, crude purity was 99.1%.

19 h (entry 9). With appropriate control of oxygen in the system, the catalyst load of $Pd(dppf)Cl_2$ could be lowered to 1 mol % and still achieve >99% conversion in 2 h (entry 5), however lower catalyst loadings (0.5 and 0.1 mol %, entries 6 and 7), led to long reaction times and decomposition of **1** was observed. Thus, for preparative runs, ~1 mol % catalyst was used, which allowed for reproducible reaction times (5−7 h) to >99% conversion of **3** (entry 10). The crude purity was also higher using the $Pd(dppf)Cl_2$ because of the significantly shorter reaction times (compare entry 1 and 10). Of practical importance, chromatographic purification of **1** was no longer required to achieve >99% purity, due to the higher-purity product obtained directly from the reaction mixture.

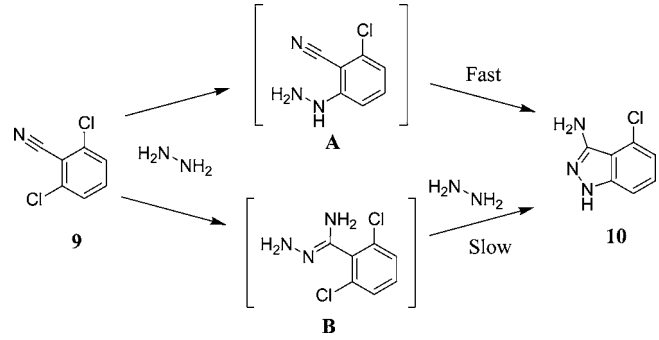
ABT-869 **1** could be isolated by biphasic extraction to remove the boron-related byproduct and inorganic base. Crystallization of the toluene extract led to the isolation of crude **1**. This crude material typically contained >500 ppm Pd residues, which could be lowered by treatment with acid-washed bentonite, followed by salt formation with HCl in EtOH. The salt was free-based using sodium phosphate, then treated with carbon (Darco G60) and/or Deloxan resin to control color and remove the remaining Pd residues to <5 ppm. The final isolation was accomplished by crystallization of **1** from EtOH/water, which produced white crystals of >99.8% purity.

While the first-generation route was successful for the production of the first kilogram quantities of **1**, the glass etching problem in the production of **3** limited the scalability of the route. A survey of other possible routes for the preparation of **3** was initiated, but other readily available 2,6-dihalobenzonitriles did not cleanly afford **3**. For example, 2-chloro-6-iodobenzonitrile and hydrazine produced a 1:1 mixture of **3** and chloro-aminoindazole **10**, and the required bromo-benzonitrile derivatives were not readily available. Other routes were briefly explored to move the Pd-catalyzed coupling to earlier in the

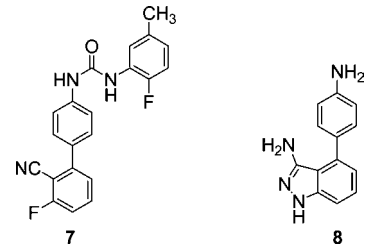
Scheme 1. **Preparation of coupling partners 3 and 6**



Scheme 2. **Chloro-aminoindazole synthesis**



synthesis. Nitrile **7** was prepared; however, the required heterocycle could not be formed. Apparently, two halogens are necessary for effective S_NAr-type amino-indazole preparation. Likewise, diamine **8** was not able to be selectively acylated using isocyanate **5**.



Second-Generation Route to 1. As the material needs for **1** grew, a scaleable, robust synthesis was required. The primary issue with the first-generation synthesis was the fluoride-induced glass etching of reactors during the synthesis of **3**. Thus, the synthesis of **1** was limited to kilo-lab scale preparations because of the hesitancy to compromise a pilot-scale reactor. One alternative would be to discover a fluoride-free preparation of **3**, but as noted above, these investigations were not productive. However, the problem was ultimately solved by changing the halogen in the Suzuki coupling from iodide to chloride.

Chloro-aminoindazole Synthesis. The chloro-aminoindazole **10** could be prepared by the reaction of hydrazine with 2,6-dichlorobenzonitrile **9** (Scheme 2).[7] Using **9** had a 2-fold benefit. First, **9** is an inexpensive, readily available starting material, and second, the fluoride etching problem is obviated. A detailed investigation of this transformation revealed that the

(7) Beck, G.; Degener, E.; Heitzer, H. *Liebigs Ann. Chem.* **1968**, *716*, 47–60.
(8) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. *J. Org. Chem.* **2006**, *71*, 8166–8172.
(9) Intermediate **A** was prepared in ref 8 and found to cyclize to **10** in 75 °C (1 h, THF solvent).
(10) Reaction calorimetry to determine ATR was done on a Mettler Toledo RC1 instrument.
(11) Adiabatic calorimetry to screen for thermal stability was done on an TIAX ARC or a VSP2 system from Fauske. See http://www.fauske.com for more information.

Table 2. **Solvent effect on reaction of 9 with hydrazine hydrate[a]**

solvent	reaction temperature (°C)	ratio (**10**:**B**)[c]	assay yield **10**[d] (%)
NMP	70	20:1	96
DMA	70	10:1	
DMSO	70	12:1	
1-butanol	100	6.0:1	
1-pentanol	100	6.9:1	
ethanol	87[b]	2.8:1	63
none	100	3.4:1	
pyridine	104	25:1	93
NMP/*n*-propanol (1:1)	103	12:1	94
1-methoxy-2-propanol	110	7.4:1	83

[a] Hydrazine hydrate (10 equiv), solvent volume (5 mL/g), reaction time= 23 h. [b] reaction temperature was refluxing solvent. [c] ratio measured by HPLC peak area at reaction completion. [d] Yields were measured by HPLC versus a reference standard.

reaction efficiency was strongly dependent on the composition of the solvent (see Table 2). In addition, two reaction pathways were identified.

In polar aprotic solvents, formation of intermediate **A**[8] is favored, which affords the product **10** in high yield. Protic solvents (alcohols and alcohol cosolvents) promoted competitive formation of intermediate **B**, which under these reaction conditions did not convert to **10**. When **B** was isolated and resubjected to the reaction conditions, **B** did not convert to **10** in the absence of excess hydrazine. However, after extended reaction times with excess hydrazine, **B** would slowly convert to **10**, probably via slow S_NAr reaction of hydrazine with **B**, followed by fast cyclization.

Two factors that may restrict cyclization of **B** is an unfavorable E/Z amino-hydrazide geometry for cyclization and the requirement for a formally disfavored 5-endo-trig cyclization. Intermediate **A** is much more reactive (favored 5-exo-dig cyclization) and is rapidly converted to **10** under the reaction conditions. However, **A** could be observed in the reaction mixture before complete consumption of **9** by LC−MS.[9]

For the best balance between reactivity and selectivity, the reaction in NMP at 70 °C was the preferred reaction conditions for scale-up. However, a safety evaluation found that the NMP process was not safe for scale-up. The adiabatic temperature rise for the reaction was 100 °C.[10] Under more sensitive adiabatic calorimetry testing (VSP2),[11] the NMP conditions showed a high risk of a runaway reaction. The heat of reaction (ATR) was sufficient to warm the reaction mass beyond the onset temperature for an uncontrolled exothermic decomposition of the reaction mixture (T_{ONSET}). The recorded maximum temperature and pressure rise rates were 1146 °C/min and 6374 psi/min, respectively. This scenario is applicable if reactor cooling is lost during the reaction. From a parallel accelerated rate calorimetry (ARC)[11] analysis, the T_{ONSET} for exothermic decomposition was 130 °C.

It was surmised that changing the reaction solvent from the high-boiling NMP (bp 202 °C) to the lower-boiling pyridine (bp 115 °C) would provide a greater heat sink between the reaction temperature and the runaway reaction temperature (T_{ONSET} = 130 °C). However, calorimetric evaluation (VSP2) of the pyridine conditions found that the reaction ATR takes the reaction mass beyond T_{ONSET}, and exothermic decomposition occurred. Thus, the switch from NMP to pyridine as solvent did not address the safety concerns with the hydrazine reaction with **9**.

Table 3. **T_{ONSET} of reaction mixture layers with added base[a]**

base additive	T_{ONSET} for exothermic decomposition: aqueous layer (°C)	pyridine layer (°C)
none (control)	134	>300
NaOAc	>300	>300
KOAc	>300	>300
Na_2CO_3	>300	>300
K_3PO_4	250	ND
K_2HPO_4	220	ND
triethylamine	205	ND
N-methylmorpholine	200	ND

[a] Reaction conditions: hydrazine hydrate (5 equiv), pyridine (5 mL/g **9**) plus base additive (2 equiv). For each entry, >95% conversion of **9** to **10** was achieved, then the layers were analyzed by DSC.

To help identify a path forward, a more in-depth safety analysis of the pyridine/hydrazine hydrate reaction was initiated. The reaction mixture is biphasic. Evaluation of both the pyridine and aqueous layers by DSC[12] revealed that the highly energetic species resided completely in the aqueous layer. As judged by HPLC and mass balance, the composition of the aqueous layer was almost exclusively hydrazine, hydrazine-HCl and any **B** that was formed. Analysis of pure **B** by DSC revealed no exotherms up to 250 °C, so the root cause seemed to be hydrazine related.

A series of base additives were examined to evaluate the effect of added base on the onset temperature of decomposition (Table 3). The results of the screen were that a wide variety of inorganic bases raised the T_{ONSET} for exothermic decomposition to >300 °C. In contrast, organic bases showed only a slight increase in the T_{ONSET} for decomposition. However, the effect of inorganic bases was not universal, K_3PO_4 and K_2HPO_4 only increased the T_{ONSET} to 250 and 220 °C, respectively.

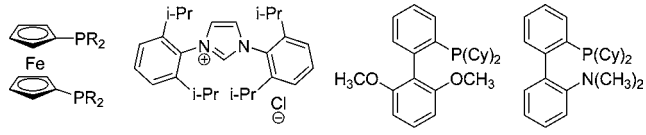
Importantly, the trend for added base increasing the T_{ONSET} observed by DSC was also observed in the adiabatic calorimetry results. The use of NaOAc in combination with hydrazine hydrate and pyridine as solvent at reflux (104 °C) had a T_{ONSET} for exothermic decomposition of 200 °C. The reaction was judged safe for scale-up to multikg scale because the observed temperature rise in VSP2 testing was not sufficient to warm the reaction mass to the T_{ONSET} for exothermic decomposition, even in a loss of cooling scenario. As an added safety margin during scale-up operations, the hydrazine was added slowly to the refluxing reaction mixture to avoid a large exotherm.

Second-Generation Suzuki Reaction. Important to the development of the second-generation Suzuki reaction was lowering the reaction temperature to less than 60 °C. As noted in the discussion of the first-generation synthesis, above this critical temperature significant degradation of **1** occurs, which directly impacts the purity of the isolated material. Despite the large body of literature around the Suzuki coupling of aryl-chlorides and heteroaryl-chlorides with boronic acids/esters,[13]

(12) Differential scanning calorimetry (DSC) was done on a Mettler DSC.

(13) For a general Suzuki review, see: Bellina, F; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. For an aryl-chloride Suzuki review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

Table 4. **Coupling conditions for 10 and 6 at 50 °C[a]**



11, R= Ph (dppf)
12, R= t-Bu (dbpf)
13, R= i-Pr (dipf)

14 **15** **16**

entry	catalyst	palladium load (mol %)	time (h)	conversion of **10** to **1** (%)
1[15]	Pd(dbpf)Cl_2 (ligand **12**)	3	19	81
2	Pd(dipf)Cl_2 (ligand **13**)	3	19	24
3	Pd(dppf)Cl_2 (ligand **11**)	3	19	8
4[16]	Pd(P*t*-Bu_3)$_2$	3	26[c]	99[e]
5	Pd$(OAc)_2$ + **15** (1:2 ratio)	3	26[c]	51[d]
6	Pd$(OAc)_2$ + **14** (1:2 ratio)	3	19	30
7[17]	Pd$(OAc)_2$ + **16** (1:2 ratio)	3	26[c]	96[d]
8	Pd(dbpf)Cl_2 (ligand **12**)	3	4	59
9	Pd$(OAc)_2$/dbpf ligand **12** (1:1 ratio)[b]	3	4	100
10	Pd$(dba)_2$ + dbpf ligand **12** (1:1 ratio)[b]	3	4	0
11	$PdCl_2$ + dbpf ligand **12** (1:1 ratio)[b]	3	4	0

[a] Reaction Conditions: **10** (1.0 equiv), **6** (1.1 equiv), K_3PO_4 (2.0 equiv), toluene, EtOH, water (1:1:1), 50 °C. [b] Catalyst solution was preformed in EtOH, by warming to 50 °C for 1 h. [c] Reaction mixture warmed to 77 °C after 19 h. [d] Conversion after 19 h at 50 °C was <10%. [e] Conversion after 19 h at 50 °C was 44%.

an emphasis was placed on finding a commercially available Pd-ligand combination that would effect the coupling of **10** and **6** in the desired temperature range.

The coupling of **10** and **6** could be achieved with a variety of catalysts at 3 mol % loading and 50 °C (see Table 4). The initial screen revealed that the electron-rich ligand palladium catalysts performed best in the coupling reaction (entries 1−7).[14]

Since temperature was an important reaction parameter, the ligand with the highest reactivity at 50 °C (**12**) was explored further (Table 4, entries 8−11). The relatively high reaction rate of precomplexed Pd(dbpf)Cl_2 catalyst (entry 8) could be improved upon by preparing the complex from Pd$(OAc)_2$ and **12** *in situ*. By precomplexation of Pd$(OAc)_2$ and **12** in a separate step of the reaction (entry 9), a large increase in the relative reaction rate could be achieved (compare entry 8 and 9).[18] The highest reaction rates were observed using a Pd:**12** mole ratio of 1:1 (varied from 1.3:1 to 0.6:1). Interestingly, the use of $Pd_2(dba)_3$ or $PdCl_2$ as the palladium source led to inactive catalysts (entries 10 and 11). Phosphorous oxidation is known in the presence of Pd$(OAc)_2$.[19] Indeed, when Pd$(OAc)_2$ and **12** were mixed in EtOH-d_6 at 50 °C, evidence of phosphorous oxides by P^{31} NMR was observed. However, nothing about the structure of the catalyst can be concluded from this data.

The superiority of the *in situ* precomplexed Pd$(OAc)_2$/dbpf ligand **12** system to the commercially available precomplexed $PdCl_2$(dbpf) system at 50 °C was clearly seen in a preparative scale run in which identical materials were used and the catalysts charged at 1 mol %. The Pd$(OAc)_2$/dbpf **12** system achieved >98% conversion of **10** to **1** over 20 h, while the $PdCl_2$(dbpf) reaction was only at 39% conversion.

The Suzuki coupling reaction of **10** and **6** was amenable to scale-up. Even though the screening experiments had been conducted in a drybox, the ligand **12** and Pd$(OAc)_2$ proved to be quite stable to air when in the solid phase. An experiment in which the solid Pd$(OAc)_2$ and **12** were exposed to air for 15 min, then used in the coupling reaction, performed within experimental error of a control reaction.

During laboratory preparations, the catalyst loading could be lowered to 1 mol % at 55 °C, however the reaction rates were slower and nonreproducible. So in practice, 1.5 to 2.0 mol % catalyst was used to achieve complete conversion of **10** in 6−8 h. In cases that the reaction time was extended, the product **1** had excellent stability at 55 °C. The source of this run to run variability was likely trace oxygen levels present during the reaction, which lead to catalyst deactivation.

Unfortunately, the coupling using the Pd$(OAc)_2$/**12** catalyst system was found to be more sensitive to the presence of oxygen than the first-generation route which utilized Pd(dppf)Cl_2. In fact, degassing the reaction solvents is critical to the success of the coupling reaction using the Pd$(OAc)_2$/**12** catalyst system. To better understand the impact of this reaction variable and as a way to develop a robust reaction, a series of oxygen studies were conducted.

Oxygen Sensitivity of the Second-Generation Suzuki Coupling. As mentioned previously, the palladium catalyzed coupling of **10** and **6** is sensitive to oxygen and it was the crucial catalyst complexation phase of the reaction that was most sensitive. To better understand this parameter, a series of experiments were conducted that examined the rate of the reaction as a function of oxygen concentration over the range 0 to 60000 ppm (Figure 1). The data reflect the oxygen level as measured in the ethanol solvent as the Pd$(OAc)_2$ and the dbpf ligand **12** were precomplexed. This catalyst mixture was then transferred into a mixture of **10**, **6** and K_3PO_4 in EtOH/water with an oxygen level of <10 ppm. The trends of the data confirm the initial observation that the Pd-coupling is sensitive to oxygen. The conversion at the 2 h time point decreases up to the 60000 ppm oxygen level.[20] The conversion data indicate that the fastest reactions were complete in less than 4 h. However, at oxygen levels as high as 10000 ppm, the reaction conversion of **10** to **1** was >98% after 24 h. The reaction stalled at oxygen levels greater than 40000 ppm, presumably through catalyst deactivation. Our conclusion

(14) For a survey of aryl-chloride Suzuki couplings in pharmaceutically relevant settings, see: Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112.

(15) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731–3734.

(16) For the use of Pd(P*t*-Bu_3)$_2$ in Suzuki reactions, see: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724; Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

(17) For a leading reference on the use of **16**, see: Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358−3366; Billingsley, K. L; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.

(18) See Itoh, T.; Toshiaki, M. *Tetrahedron Lett.* **2005**, *46*, 3573–3577; the Pd$(OAc)_2$/**12** catalyst system is similar to that used by Itoh, but precomplexation was not required in that case.

(19) It is known that a combination of Pd$(OAc)_2$ and phosphines lead to phosphine oxide formation. See: Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013. Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177–2180.

(20) There was significant scatter in the data at the 2 h time point. The 24 h conversion data is more important for definition of the critical oxygen concentration.

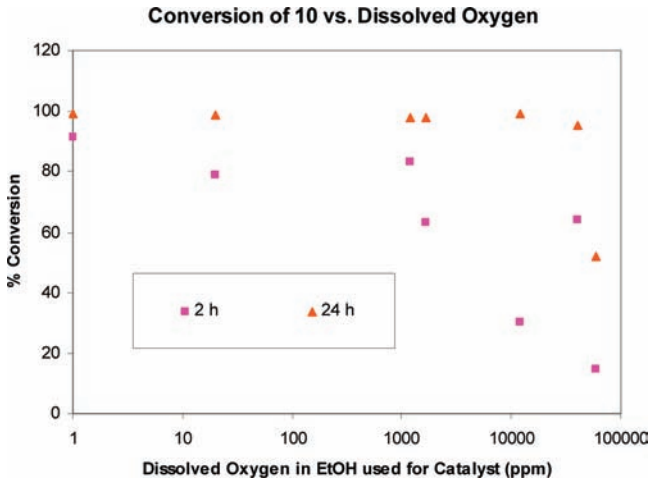
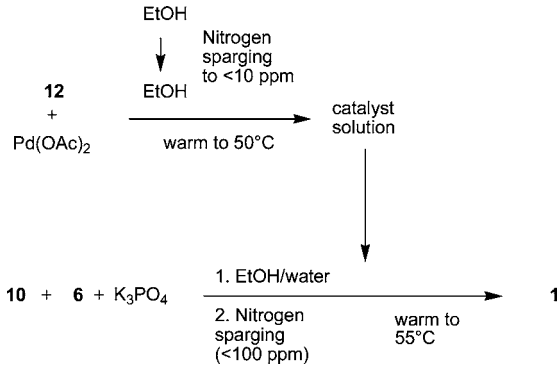


Figure 1. **Effect of Oxygen Level on Conversion of 10 to 1.**

Scheme 3. **Final reaction diagram of Suzuki reaction using oxygen analysis as a PAT**



is that the critical level for oxygen in the catalyst precomplexation phase is at 10000 ppm oxygen.

Pilot-Scale Synthesis of 1. With a better understanding of the sensitivity of the Suzuki reaction to oxygen, the Suzuki coupling was scaled up to 40 kg, using a headspace oxygen monitor[21] to guide the degassing operations (Scheme 3). A solution of EtOH/water was degassed to <10 ppm oxygen (headspace) by bubbling and then added to $Pd(OAc)_2$ and **12** for catalyst complexation. The catalyst solution was charged to a degassed (<100 ppm oxygen, headspace) mixture of **10**, **6** and K_3PO_4 in EtOH/water. After 1.5 h at 55 °C, the reaction had achieved >99.9% conversion of **10** to **1**. The reaction rate was consistent with the best lab results for coupling of **10** and **6**. On the basis of the excellent reaction rate observed, the use of the headspace analyzer to monitor the level of oxygen during the process was considered a success.

Conclusion

The development and scale-up of a safe, practical chemical synthesis of ABT-869 **1** has been achieved. The issues with the scalability of the first-generation synthesis (glass etching, reaction temperature >60 °C) were solved by development of the second-generation synthesis. The initially observed safety issue with the hydrazine condensation reaction to form **10** was solved by making appropriate changes to the reaction conditions (solvent and addition of base) that gave a sufficient safety margin to allow the safe scale-up without danger to personnel and pilot facilities. A catalyst preparation was discovered that features remarkable reactivity in the case of coupling chloride **10** and boronate **6**, which allows >99.9% conversion (>95% yield) at 55 °C. The Suzuki coupling is a highly reproducible process controlled by an oxygen analyzer as a PAT. The second-generation route was successfully demonstrated on 40 kg scale in pilot equipment in 62% overall yield.

(21) See the Supporting Information for a discussion of the apparatus and the method of estimating the required sparge time to reach the necessary dissolved oxygen level from the headspace measurement.

Experimental Section

General. Compounds **2**, **4**, **5**, and **9** are commercially available. Filterol GR is available from BASF catalysts, LLC. Acticarbone CPL is available from Arkema, Inc.

4-Iodo-1H-indazol-3-amine (3). 2-Fluoro-6-iodobenzonitrile **2** (5.0 kg, 20.2 mol) and $NaHCO_3$ (2.6 kg, 31 mol) were suspended in ethanol (19.8 kg). Hydrazine monohydrate (5.0 kg, 99.9 mol) was added; the resulting mixture was heated to reflux and stirred for 8 h. After cooling to 25 °C, water (50.1 kg) was added; the resulting slurry was stirred at 25 °C for 2 h and at 0 °C for 2 h. The product was collected by filtration, washed with water (4 × 5.0 kg) and dried under vacuum at 65 °C for 16 h to afford 4.92 kg (94%) as a pale-yellow solid. MP: 152−154 °C. ^{1}H NMR (DMSO-d_6) δ 5.04 (s, 2 H) 6.91 (dd, J = 8.4, 7.1 Hz, 1 H) 7.19−7.45 (m, 2 H) 11.78 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 85.6, 109.8, 114.2, 127.3, 127.9, 141.0, 148.0. IR (KBr) 3304, 1604, 1525, 1339, 805, 743 cm^{-1}. MS (ESI): 259.7 *m/e* (M + H). Anal. Calcd for $C_7H_6IN_3$: C 32.46, H 2.33, N 16.22; found C 32.38, H 2.13, N 16.16.

4-Chloro-1H-indazol-3-amine (10). 2,6-Dichlorobenzonitrile **9** (50.0 kg, 267 mol) and NaOAc (26.2 kg, 319 mol) were suspended in pyridine (216 kg), and the mixture was heated to 100 °C. Hydrazine monohydrate (150 kg, 3000 mol) was added slowly over 30 min, and the reaction mixture was stirred at 105 °C for 16 h. After cooling to 30 °C, water (595 kg) was added and the resulting solution filtered. The product **10** was crystallized by the addition of water (184 kg), seeding with a slurry of product (280 g of seeds in 6.5 kg water), the addition of more water (1746 kg) and cooling to 0 °C. The product was collected by filtration, washed with water (2 × 100 kg) and dried under vacuum at 60 °C for 16 h to afford 38.0 kg (74%) as a white solid. MP: 163−165 °C. ^{1}H NMR (DMSO-d_6) δ 5.18 (s, 2 H) 6.87 (d, J = 7.1 Hz, 1 H) 7.08−7.26 (m, 2 H) 11.84 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 108.6, 110.4, 117.6, 125.2, 127.0, 142.3, 147.6. IR (KBr) 3337, 1618, 1606, 1527, 1351, 829, 782 cm^{-1}. MS (ESI): 167.9 *m/e* (M + H). Anal. Calcd for $C_7H_6ClN_3$: C 50.17, H 3.61, N 25.07; found C 50.04, H 3.42, N 25.11.

1-(2-Fluoro-5-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (6). To a suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4** (9.9 kg, 45.2 mol) in toluene (104 kg) was added 2-fluoro-5-methylisocyanate **5** (7.8 kg, 51.6 mol), and the resulting mixture was heated to 50 °C and stirred for 2 h. After cooling to 20 °C and stirring the mixture for 1 h, the crystallized product was collected by filtration and washed with toluene (2 × 30 kg).

The crude wet cake was suspended in acetonitrile (235 kg) and a small sample (2 L) retained for seeds. The product was recrystallized by heating the suspension to 70 °C to dissolve the solid, cooling to 65 °C and seeding with the sample from above, and cooling to −5 °C over 18 h. The product **6** was collected by filtration, washed with acetonitrile (2 × 20 kg) and dried under vacuum at 60 °C for 16 h to afford 14.9 kg (89%) as a white solid. MP: 200−202 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 12 H) 2.25 (s, 3 H) 6.72−6.82 (m, 1 H) 7.06 (dd, J = 11.3, 8.3 Hz, 1 H) 7.47 (d, J = 8.5 Hz, 2 H) 7.59 (d, J = 8.5 Hz, 2 H) 7.97 (dd, J = 7.9, 2.0 Hz, 1 H) 8.49 (d, J = 2.5 Hz, 1 H) 9.17 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 20.9, 24.8, 83.2, 114.1 (d, J = 19.18 Hz), 116.0, 116.7, 120.6, 122.4 (d, J = 7.7 Hz), 126.5 (d, J = 10.7 Hz) 133.1 (d, J = 3.0 Hz) 135.1, 141.9, 149.8 (d, J = 237.4 Hz), 151.4. IR (KBr) 3387, 1669, 1553, 1397, 1357, 814, 654 cm^{-1}. MS (ESI): 371.0 *m*/*e* (M + H). Anal. Calcd for $C_{20}H_{24}BFN_2O_3$: C 64.88, H 6.53, N 7.57; found C 65.04, H 6.57, N 7.60.

1-(4-(3-Amino-1H-indazol-4-yl)phenyl)-3-(2-fluoro-5-methylphenyl)urea (1). *First-Generation Process.* To a suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4** (10.7 kg, 48.8 mol) in toluene (100 kg) was added 1-fluoro-5-methylphenylisocyanate **5** (7.7 kg, 50.9 mol), and the resulting mixture was warmed to 50 °C and stirred for 1 h. After cooling to 25 °C, the excess isocyanate was quenched with ethanol (26 kg), and the mixture was allowed to stir for 30 min.

4-Iodo-1*H*-indazol-3-amine **3** (10.6 kg, 40.9 mol), sodium carbonate (10.0 kg, 94.3 mol) and 1,1-bis (diphenylphosphino) ferrocene palladium dichloride (400 g, 0.49 mol) were suspended in the mixture from above, ethanol (75 kg) and water (100 kg). The resulting mixture was purged of oxygen by bubbling nitrogen through for 30 min. The reaction was heated to reflux and stirred for 6 h. After cooling to 20 °C, EtOAc (300 kg) and 20% NH_4Cl in water (80 kg) were added, and the mixture was stirred for 30 min and allowed to settle for 30 min, and the bottom layer was discarded. The organic layer was washed with 20% NH_4Cl in water (160 kg) and water (100 kg) by mixing together for 30 min, settling for 30 min and discarding the lower layers. The organic layer was then treated with Filterol GR (15 kg) for 4 h and filtered. The organic layer was distilled under reduced pressure (5−10 Torr) to ∼180 L. The distillation was continued and the solvent level maintained at 180 L with continuous addition of toluene (240 kg), during which the product crystallized. After cooling the product slurry to 20 °C, the product was collected by filtration, washed with toluene (2 × 80 kg) and dried under a flow of nitrogen for 1 h. The product wet cake was dissolved in EtOAc (400 kg) and EtOH (175 kg), treated with Filterol GR (10 kg) for 4 h and filtered. Concentrated HCl (7.0 kg) was added to the filtrate, and after stirring at 20 °C for 4 h the volume was reduced to half by vacuum distillation (5−10 Torr). The product HCl salt was collected by filtration, washed with EtOAc (2 × 30 kg) and dried under vacuum at 50 °C for 16 h to afford 9.3 kg (57%) as a white solid.

The HCl salt was suspended in EtOAc (300 kg) and EtOH (130 kg) and washed with a solution of $Na_2HPO_4 \cdot 7H_2O$ (7.5 kg) in water (225 kg) and a solution of NaH_2PO_4 (4.0 kg) in water (225 kg). The resulting solution of freebase was treated with Darco G60 carbon (1.5 kg) for 4 h and then filtered. The resulting solution was distilled under reduced pressure (5−10 Torr) to ∼300 L. The distillation was continued and the solvent level maintained at 300 L with continuous addition of EtOH (605 kg). The resulting suspension was heated to 70 °C to dissolve the bulk of the material and cooled to 20 °C; the crystallization was completed by the addition of water (375 kg). The product was collected by filtration, washed with water (2 × 50 kg) and dried under vacuum at 70 °C for 4 h to afford 7.9 kg (46%) as a white solid.

Second-Generation Process. 4-Chloro-1*H*-indazol-3-amine **10** (21.6 kg, 129 mol), 1-(2-fluoro-5-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea **6** (50.0 kg, 135 mol) and K_3PO_4 (54.7 kg, 260 mol) were suspended in water (165 kg) and ethanol (345 kg) which was purged of oxygen (<100 ppm, Alpha-Omega Oxygen Analyzer, series 3000) by bubbling nitrogen through the mixture before addition to the solids. The catalyst solution was prepared by first purging ethanol (55 kg) to <10 ppm oxygen by bubbling with nitrogen, then adding the ethanol to a combination of $Pd(OAc)_2$ (580 g, 2.6 mol, 2 mol %) and 1,1′-bis(di-*tert*-butylphosphino)ferrocene (1.22 kg, 2.6 mol, 2 mol %) and heating the mixture to 55 °C for 45 min. The catalyst was then transferred to the suspension of reactants and the reaction mixture heated to 55 °C for 1.5 h. After cooling to 20 °C, EtOAc (1100 kg) and 20% NH_4Cl in water (170 kg) were added, and the mixture was stirred for 30 min and allowed to settle for 30 min, and the bottom layer was discarded. The organic layer was washed with 20% NH_4Cl in water (410 kg) and water (270 kg) by mixing together for 30 min, settling for 30 min, and discarding the lower layers. The organic layer was distilled under reduced pressure (5−10 Torr) to ∼600 L. The distillation was continued and the solvent level maintained at 600 L with continuous addition of toluene (820 kg), during which the product crystallized. After cooling the product slurry to 20 °C, the product was collected by filtration, washed with toluene (2 × 260 kg) and dried under a flow of nitrogen for 1 h. The product wet cake was suspended in EtOAc (1380 kg) and EtOH (300 kg), and conc. HCl (102 kg) was added. After stirring at 20 °C for 4 h, the product HCl salt was collected by filtration, washed with EtOAc (2 × 100 kg) and dried under vacuum at 50 °C for 16 h to afford 49.0 kg (92%) as a white solid.

The HCl salt was suspended in EtOAc (1200 kg) and EtOH (525 kg) and washed with a solution of $Na_2HPO_4 \cdot 7H_2O$ (46 kg) in water (1335 kg) and a solution of NaH_2PO_4 (23 kg) in water (490 kg). The resulting solution of freebase was filtered through a 0.5 μm in-line filter and treated with Filterol GR (41 kg) for 4 h. After filtration, the solution was treated with Acticarbone CPL carbon (9 kg) for 4 h and then filtered. The resulting solution was distilled under reduced pressure (5−10 Torr) to ∼1300 L. The distillation was continued and the solvent level maintained at 1300 L with continuous addition of EtOH (2720 kg). EtOH (560 kg) was added to the resulting suspension, and it was heated to 50 °C to dissolve the bulk of the material and cooled to 20 °C, and the crystallization was completed by the addition of water (1280 kg). The product was collected by filtration, washed with water (2 × 200 kg) and dried under vacuum at 70 °C for 4 h to afford 40.9 kg (84% overall yield)

as a white solid. Mp: 209−211 °C. ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3 H) 4.35 (s, 2 H) 6.70−6.86 (m, 2 H) 7.07 (dd, J = 11.3, 8.4 Hz, 1 H) 7.26 (d, J = 3.7 Hz, 2 H) 7.36−7.46 (m, 2 H) 7.60 (d, J = 8.5 Hz, 2 H) 8.00 (dd, J = 7.9, 2.0 Hz, 1 H) 8.53 (d, J = 2.5 Hz, 1 H) 9.20 (s, 1 H) 11.72 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 21.0, 108.3, 110.2, 114.2 (d, J = 18.8 Hz) 117.7, 118.8, 120.7, 122.4 (d, J = 7.3 Hz), 126.0, 126.6 (d, J = 10.2 Hz), 129.0, 132.5, 133.1 (d, J = 3.4 Hz) 135.0, 138.6, 141.7, 147.7, 149.8 (d, J = 237.0 Hz), 151.7. IR (KBr) 3241, 1689, 1607, 1548, 1316, 1228, 794 cm^{-1}. MS (ESI): 376.0 m/e (M + H). Anal. Calcd for $C_{21}H_{18}FN_5O \cdot 0.25C_2H_6O$: C 66.74, H 5.08, N 18.10; found: C 66.60, H 4.83, N 18.31.

Acknowledgment

We thank Ana Misetic, Kevin Gernhardt, Lalit Bavda and Brenda Mathias for analytical support.

Supporting Information Available

More detail about the solution- and vapor-phase determination of oxygen levels; parametric model of the deoxygenation kinetics of lab-scale reactors. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review August 8, 2009.

OP900208Y