Organic Process Research & Development **2003**, *7*, 733–742

A Practical Synthesis of 6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline and the Art of Removing Palladium from the Products of Pd-Catalyzed Reactions

Kurt Königsberger, Guang-Pei Chen, Raeann R. Wu, Michael J. Girgis, Kapa Prasad,* Oljan Repič, and Thomas J. Blacklock

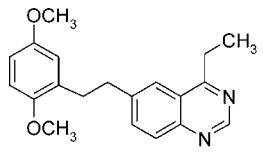
Process Research and Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Abstract:

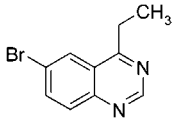
A concise large-scale synthesis of 1, a new antimitotic agent is described. The key step was a one-pot Sonogashira cross-coupling of an aryl halide with a heteroaryl halide through an acetylene using the readily available 2-methyl-3-butyn-2-ol (7). An innovative approach for palladium removal was designed and successfully scaled-up on a multikilogram scale. The product was crystallized from the crude reaction mixture while keeping the residual palladium in the mother liquor by using Pd-scavenging agents such as *N*-acetylcysteine or thiourea.

Introduction

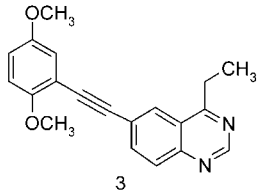
Compound **1** is an antimitotic agent,[1] which inhibits the proliferation of human epidermal cells, and it is being developed for topical treatment of hyperproliferative skin disorders with an improved therapeutic window and a reduced side-effect profile relative to the current standard treatment, i.e., topical treatment with 5-fluorouracil or surgical treatment. The first plant campaign was completed with the preparation of 3 kg of drug substance, and the second plant campaign was completed with the delivery of 50 kg of drug substance with an overall yield of 59% based on **2** by using an optimized Sonogashira coupling reaction[2] as the key step for making the unsymmetrical bisarylethyne **3**.



1



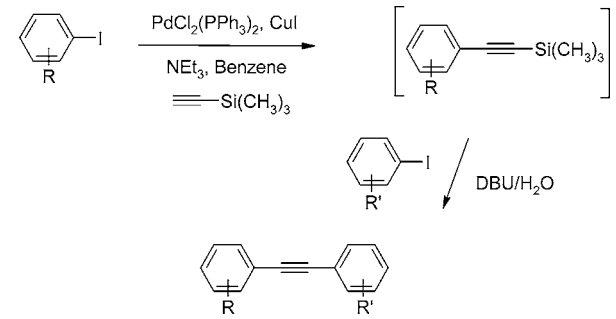
2



3

In general, for the preparation of diarylethynes the method of choice is the Sonogashira reaction, which involves palladium-catalyzed cross coupling of a protected acetylene with an aryl halide, followed by a deprotection and coupling with the same aryl halide in the case of symmetrical diarylethyne or a different aryl halide for obtaining an unsymmetrical ethyne. Recently Grieco and co-workers[3a] published a one-pot synthesis applicable to both symmetrical and unsymmetrical ethynes using trimethylsilylacetylene ($5760/kg, Aldrich) and DBU/water for the in situ removal of the silyl group as shown in Scheme 1. This concept can be traced back to the in situ method introduced by Mori and co-workers earlier.[3b] We accomplished a similar one-pot preparation of **1** with a much less expensive and readily available acetone adduct of acetylene, namely **7** ($55/kg, Aldrich) in a more efficient manner, and these results are presented here.

Scheme 1



The original synthesis of **1** employed by medicinal chemists[1] is shown in Scheme 2. This synthesis involves a Pd-catalyzed coupling of aryl acetylene **5** with heteroaryl halide **2** followed by hydrogenation. The aryl acetylene **5** was generated by a Wittig olefination, and a chromatographic purification was necessary as triphenylphosphine oxide was formed as a byproduct in stoichiometric amounts. This was a scale-up problem. However, the coupling of acetylene **5** with **2** as reported in the original synthesis could be retained for large-scale work. On the basis of a retrosynthetic analysis, of **5** we came up with commercially available **6** (bulk price <$120/kg, from Alfa Aesar) and acetylene **7** coupled under Sonogashira Pd-catalyzed conditions (Scheme 3). The use of **7** has been reported earlier for making diarylacetylenes by Rossi and co-workers.[4] Thus, our objectives were (i) to

(1) Nussbaumer, P. WO 9628430, 1996.
(2) Sonogashira, K.; Tohada, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(3) (a) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. C.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199−3202. (b) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780.
(4) (a) Carpita, A.; Lessi, A.; Rossi, R. Synthesis, **1984**, 571. (b) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763.

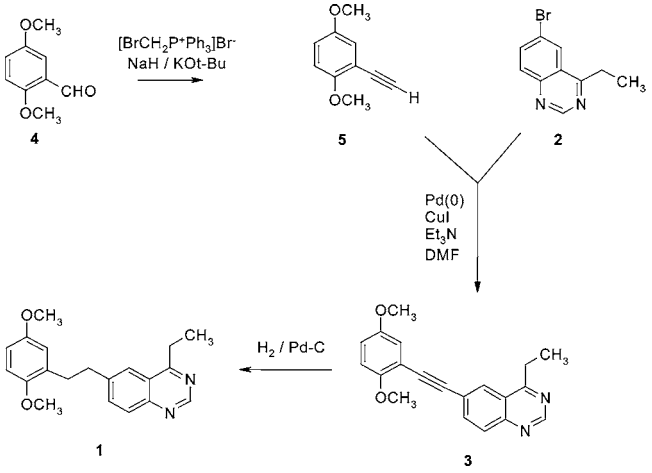
10.1021/op034072x CCC: $25.00
Published on Web 08/20/2003

Table 1. **Pd-catalyzed cross-coupling of 6 and 7[a]**

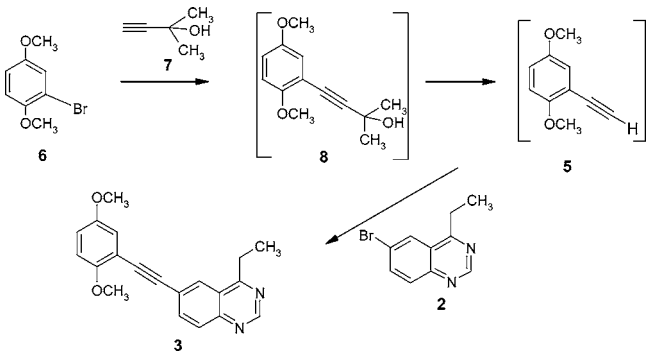
entry	ligand [equiv]	Pd source [equiv]	base [equiv]	conditions	observations	yield (%)
1	$Pd(PPh_3)_4$ [0.01]		DIPA [3]	toluene, 76 °C, 19 h	gets darker over time	92
2	PPh_3 [0.04]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 20 h	gets darker over time	95
3	Dppdpe [0.02]	$Pd(OAc)_2$ [0.01]	DIPA [3]	toluene, 78 °C, 12 h	slow at 60 °C, at 78 °C faster, lighter color	95
4	TPPTS [0.02]	$Pd(OAc)_2$ [0.005]	NEt_3 [3]	CH_3CN/H_2O, 80 °C, 8 h	yellow solution, gets brownish	99
5	TPPMS [0.03]	$Pd(OAc)_2$ [0.01]	NEt_3 [3]	CH_3CN/H_2O, 80 °C, 3 h		98
			Optimization of Ligand Amount			
6	PPh_3 [0.02]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 16 h	black color	35
7	PPh_3 [0.044]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 12 h	gets somewhat darker over time	95
8	PPh_3 [0.05]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 20 h	stays light in color	92.5
			Optimization of Cuprous Iodide Amount			
9	PPh_3 [0.044] CuI [0.004]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 16 h	stays light in color	80
10	PPh_3 [0.044] CuI [0.025]	$PdCl_2$ [0.01]	DIPA [3]	toluene, 78 °C, 4 h	gets black, slow rate	33

[a] All reactions run with bromide (1 equiv), DIPA (3 equiv), alkyne (1.5 equiv), CuI (0.01 equiv), toluene, at 78 °C, except where noted.

Scheme 2. **Original synthesis**



Scheme 3. **Conversion of 6 to 3**



screen and identify an efficient but less expensive catalyst; (ii) to find in situ deprotection conditions after the first coupling so that the second coupling can be done in the same reactor without spending additional Pd catalyst; (iii) simplification of the workup procedure to arrive at acceptable Pd levels in the product as this will influence the acceptability of the drug substance for further pharmaceutical processing.

First Coupling Step

A survey of raw materials which could act as a source for Pd^0 revealed $PdCl_2$ as the cheapest precatalyst, followed by $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$. Prices of the preformed Pd^0 catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ are obviously higher. Initially we also screened other catalytic systems such as Pd/C with or without added phosphines[5,6] and more expensive palladocycles such as the Bedford catalyst[7] and the Herrmann catalyst[8] with no advantage. The best results obtained in our screening experiments on Sonogashira cross-coupling of **6** and **7** are shown in Table 1.

At the start of these investigations,[9] we checked the usefulness of water-soluble sulfonylated phosphine complexes such as TPPTS[10] and TPPMS[11] as ligands (see Scheme 4) with the hope of limiting the Pd-contamination in reaction products and found that the combination of TPPTS or TPPMS and $Pd(OAc)_2$ in acetonitrile/triethylamine at 80 °C, in the presence of water, catalyzed the cross coupling of **6** and **7** efficiently and very cleanly even at a catalyst loading

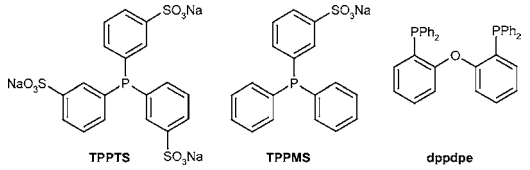
(5) (a) Bleicher, L.; Cosford, N. P. *Synlett* **1995**, 1115. (b) De la Rosa, M. A.; Velarde, E.; Guzman, A. S*ynth. Commun.* **1990**, *20*, 2059.
(6) Ennis, D. E.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248.
(7) Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793. Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *J. Chem. Soc., Chem. Commun.* **1998**, 2095.
(8) Beller, M.; Reisinger, C. P.; Herrmann, W. A. DE 195 15 444 C 1, 1996.
(9) Palladium-catalyzed coupling of **7** with 2-bromo-1,4-bis(methoxymethoxy)-benzene was reported earlier (ref: Pinault, M.; Frangin, Y.; Genet, J.-P.; Zamarlik, H. *Synthesis* **1990**, 935−937).
(10) Kuntz, E. G. U.S. Patent 4,248,802, 1981. Sinou, D. *Bull. Soc. Chim. Fr.* **1987**, *3*, 480−486.
(11) Ahrland, S.; Chatt, J.; Davies, N. R.; Williams, A. A. *J. Chem. Soc.* **1958**, 276−288.

Table 2. **Examples of the second coupling step**

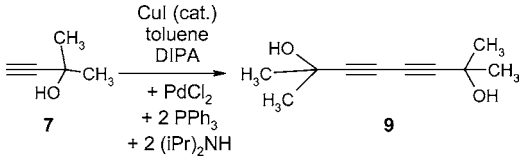
entry	ligand/Pd source (equiv)	base (equiv)	conditions	observations	yield (from **5**)
1	$Pd(PPh_3)_4$ (0.0025) CuI (0.025)	NaOH (1.4)	isolated **8**; toluene; azeotropic distillation of water, 104−110 °C; 1 h	gets dark red/brown; bumping/foaming; crusts on reactor walls	75.2% yield 98.4% pure
2	no additional[a] catalyst	NaOH (2.6)	reaction mixture after first coupling step; distilled off water as azeotrope, 104−110 °C; 5 h	gets dark red/brown; bumping/foaming; crusts on reactor walls	65% yield
3	no additional catalyst	NaOH (3) Bu_4NBr (0.02)	reaction mixture after first coupling step; distilled off water as azeotrope, water; 84−85 °C;3−5 h	gets dark red/brown; grey solid precipitates	75.1% yield 97.8% pure

[a] The first step is run as previously described. The extra diisopropylamine and **7** were distilled off. A degassed mixture of **2** in toluene was added, followed by other reagents (see table).

Scheme 4. **Ligands mentioned in Table 1**



Scheme 5. **Oxidative dimerization of 7**



of 0.5 mol %. This catalytic system gave a much cleaner reaction than Pd(II) salt/PPh_3 combinations. Reactivity depended strongly on the water content of the medium; the best reactivity was obtained with the right amount of water needed to barely keep the reaction mixture homogeneous (acetonitrile:water 56:44; 8.7 g of **7**/100 mL). However, the high price and limited commercial availability of these ligands prompted us to reject this system as a choice at present.

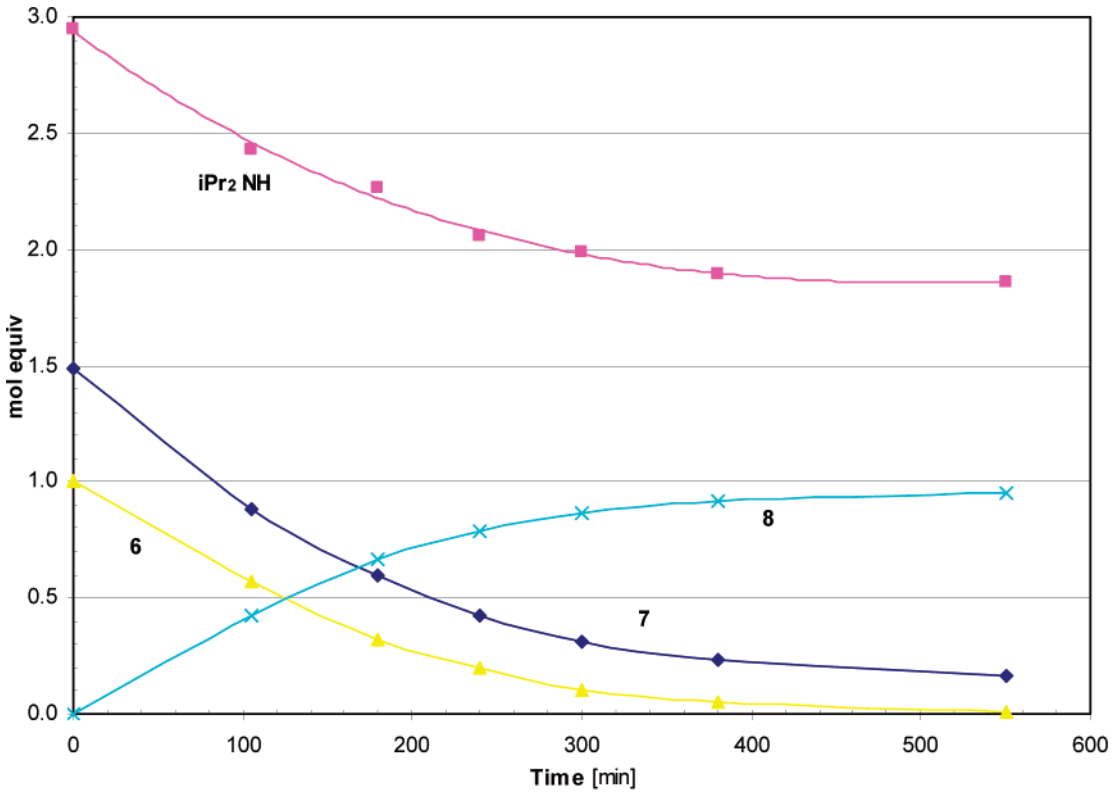
Of the other conditions, we excluded $Pd(OAc)_2$/dppdpe (Table 2, entry 3) because of the high price and limited availability of the ligand. This led to the obvious selection of the $PdCl_2/PPh_3$ combination (Table 2, entry 2) for further study. Under these conditions, the reaction rate, completeness, and the extent of byproduct formation strongly depended on the Pd-to-phosphine ratio used. At a ratio of 1:2, the reaction becomes black and is incomplete. Best results were obtained between 1:4 and 1:5, and a ratio of 1:4.4 was chosen for the process conditions. Pd/CuI ratios from 1:0.4 to 1:2.5 were tried, and a ratio of 1:1 appeared to be the optimum.

Degassing of the reactant solution was found to be crucial for the success of the reaction. Insufficient degassing led to higher amounts of byproducts and incomplete reaction due to deactivation of the catalyst. Several sequences of degassing of the reaction components and setting up of the reaction were tested. Their application depended primarily on the type of plant reactor train and individual preferences. Originally, a mixture of **6**, diisopropylamine, $PdCl_2$, PPh_3, and CuI in toluene was degassed by evacuation at room temperature, followed by stirring under nitrogen for 10 min. This was repeated four times. **7** was then added and the mixture heated to 78 °C. Later, on the basis of prior manufacturing experience with other projects, degassing by reflux was used. Thus, a solution of **6**, **7**, and diisopropylamine in toluene was degassed by heating at reflux for 30 min while sweeping the headspace with nitrogen. After cooling to 45−50 °C, $PdCl_2$ and PPh_3 were added and stirred for 15−30 min to dissolve $PdCl_2$. CuI was added, and the mixture was heated to 78 °C. In our pilot-plant setting, $PdCl_2$ was replaced with $Pd(PPh_3)_2Cl_2$ (another air-stable Pd(II) and soluble reagent), as $PdCl_2$ is very dense, and it was assumed that in a glass-lined pilot-plant vessel $PdCl_2$ would accumulate in the cup-shaped area above the bottom outlet valve and not mix with the reaction mixture. Therefore, the final sequence of additions was as follows:

An auxiliary vessel was charged with **6**, diisopropylamine, and toluene; the mixture was degassed by heating at reflux for 30 min while sweeping the headspace with nitrogen. The mixture was cooled and transferred with nitrogen pressure into the inerted main reactor, containing $Pd(PPh_3)_2Cl_2$, PPh_3 and CuI. After stirring for 30 min to dissolve most of the catalyst, **7** was added to the cloudy, reddish mixture, which turned yellow and lightened up as it was heated to 78 °C.

The color change of the reaction mixture from reddish to yellow can be explained by a reduction of Pd(II) to Pd^0, accompanied by an oxidative coupling of **7** as shown in Scheme 5. Residual oxygen in solution may at this point reoxidize Pd^0 and lead to increased formation of **9**. This side-reaction necessitated the degassing of all liquid components before they were brought in contact with the catalyst. Additionally, some triphenylphosphine oxide (<1 equiv, vs Pd) was formed (detected by GC/MS) during this phase of catalyst activation.

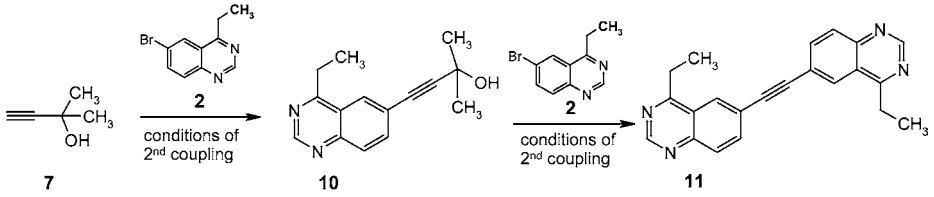
After heating the reaction mixture to 78 °C, the reaction proceeded smoothly to completion over a 10−15 h period (typically12−13 h has been observed in the laboratory). Figure 1 shows the reactant and product concentration profile during the conversion. Approximately 80% of the conversion occurred within the first 4 h.



Catalyst: $PdCl_2$ (0.01 equiv), PPh_3 (0.044 equiv), CuI (0.01 equiv). Data were obtained by GC and are response-corrected, using cumene as an internal standard in the reaction mixture.

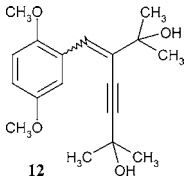
Figure 1. **Concentration profiles of reactants 6, 7, and product 8 in the coupling reaction.**

Scheme 6. **Byproducts derived from 2 and residual 7**



The first coupling step having been accomplished in a satisfactory manner, the issue next addressed was the in situ deprotection of **8** followed by coupling with **2** without adding extra palladium reagent. The one component in the reaction mixture that is incompatible with the second coupling is **7**, which has to be removed as it will participate in the reaction with **2** to form byproducts as shown in Scheme 6.

These byproducts were prepared independently as reference standards. Compound **10** was detected in the crude reaction mixture after the second coupling step, and **11** was found to be insoluble in common organic solvents. Of the 1.5 equiv of **7** used only approximately 0.15 equiv remained after the first coupling reaction. Several pathways for the consumption of **7** have been discovered. Whereas after catalyst activation, no additional dimeric acetylene **9** was formed, a compound with a mass of 304 was detected by GC/MS and partially purified from the reaction mixture. It was assigned structure **12** on the basis of literature precedence.[12] Presumably, this product is formed by a carbopalladation mechanism analogous to the one described in ref 12 for a similar coupling product. Approximately 3−5% of this impurity has been detected. The rest of the unaccounted **7** was assumed lost via a polymerization pathway forming oligomeric material. Distillation was found to be effective for removal of the remaining **7**. Concentration of the reaction mixture to 40−45% of the original volume, followed by flushing with a similar volume of degassed toluene, removed **7** reproducibly to less than 1 mol % vs product **8**.



(12) (a) Gonzalez, J. J.; Francesch, A.; Cardenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, *63*, 2854. (b) Stara, I. G.; Stary, I.; Kollarovic, A.; Tepy, F.; Saman, D.; Fiedler. P. *Tetrahedron* **1998**, *54*, 11209.

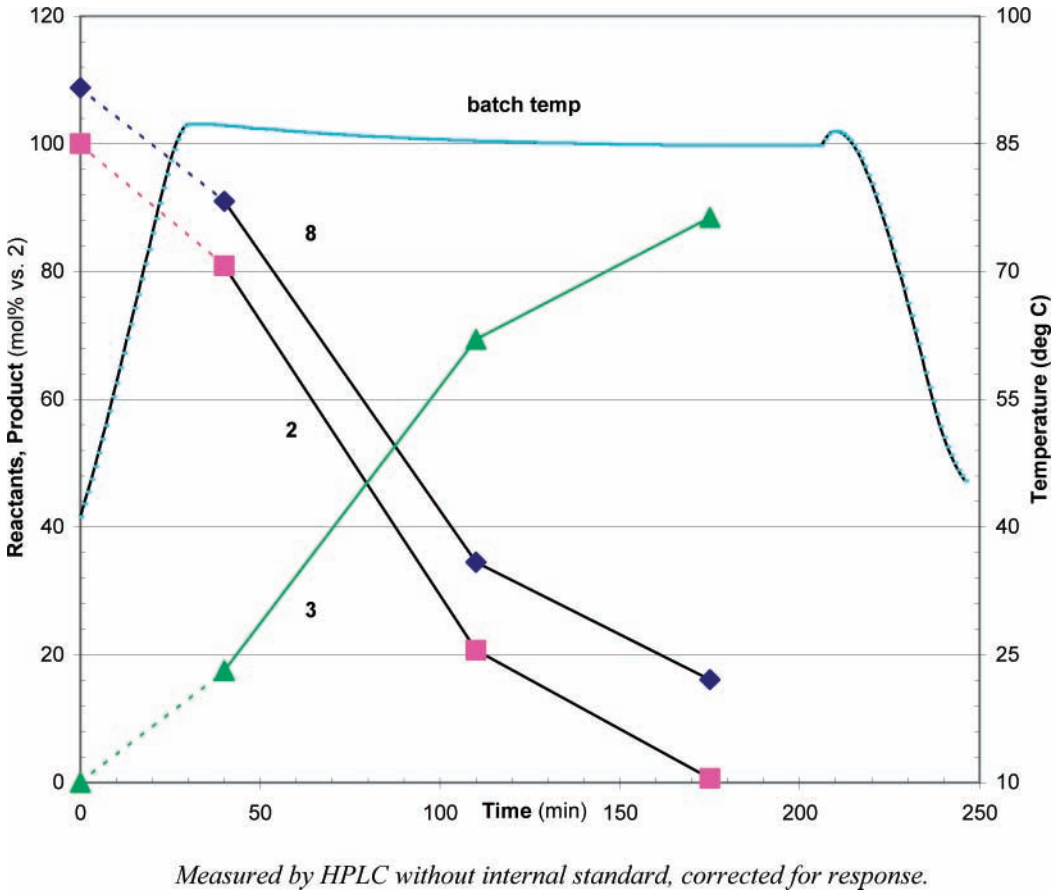


Figure 2. **Concentration profile of reactants 8, 2, and product 3 over the course of the second coupling step.**

Second Coupling Step

Initially the coupling of **2** was studied with isolated **8** (Scheme 3). This was conducted with solid NaOH in the presence of 0.25 mol % $Pd(PPh_3)_4$ and CuI (Table 2, entry 1) while removing water azeotropically from refluxing toluene. With the crude reaction mixture of **8** (after distilling off **7**), the second coupling was a bit slow but went to completion in 5 h. However, removal of water, generated during the reaction by azeotropic distillation, was difficult to accomplish due to the presence of diisopropylammonium bromide present from the first coupling step. Nevertheless success was achieved when the reaction was run in a biphasic system (aqueous NaOH/toluene) in the presence of tetrabutylammonium bromide, affording **3** in 68−75% isolated yield.

Thus, the second coupling step was conducted as follows: Compound **2** (88 mol % with respect to **6**) and Bu_4NBr were dissolved in toluene/water and degassed by heating at reflux (88 °C) for 30 min, while purging the headspace with a slow stream of nitrogen. After cooling to ambient temperature, the mixture was transferred to the vessel containing the concentrated reaction mixture of **8** using nitrogen pressure. Aqueous 50% sodium hydroxide was added, and the reaction was heated at reflux while stirring vigorously. Because of the formation of 1 equiv of acetone, the boiling point of the mixture dropped by approximately 3 °C over the course of the reaction. As the reaction progressed, the color of the mixture deepened from yellow to dark red/brown. The rate of reaction was dependent on the mixing; apparently the tetrabutylammonium-mediated hydroxide ion transport between aqueous and organic phase was the rate-limiting step. In the laboratory, **5** was not detectable after 3 h, depending on the reactor geometry and the stirring rate. Using curved blade impellers in the LabMax 2-L vessel, tip-speeds of 1.2−1.6 m/s were applied (300−400 rpm, 3-in. diameter). Under these conditions, the mixing was judged suboptimal due to a lack of efficient baffles in the LabMax vessel. In the plant, efficient baffles and much higher tip-speeds (5−6 m/s) led to improved reaction rates (less than 2 h). Figure 2 shows the concentrations of reactants over the course of a typical reaction.

Table 3. **Equilibration experiments to remove phosphinoxide**

adsorbent	weight [%]	time [h]	PPh═O Level[a] [dissolved]
alumina basic	66	24	no change
alumina neutral	66	24	no change
alumina acidic	66	24	no change
charcoal Darco G60	33	24	no change
silica gel 150 Å	66	12	no change
Panther Creek Clay	100	0.5	70% decrease
(Southern Bentonite)		4	90% decrease

[a] **Note:** $O{=}PPh_3$ levels were analyzed by GC.

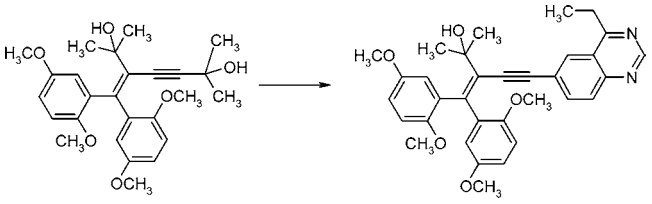
There is a significant discrepancy between the amount of **2** consumed and the amount of **3** formed as evidenced by the crude yield (determined analytically by measurement of the concentration of **3** in the crude reaction mixture) of 78−85%. Several byproducts are visible in the HPLC of the crude

Table 4. **Influence of adsorption additives on Pd and phosphorus levels in 3**

entry	adsorbent (weight/weight of expected product)	Pd levels in solution [ppm][a] 6 h stirring	Pd levels in solution [ppm][a] 24 h stirring	yield[b] [%]	purity [%]	Pd [ppm]	P [ppm]
1	–		173	69	98.4	443	87
2	Panther Creek Clay (200%)	74	60	60	99.6	111	19
3	Panther Creek Clay (200%) + Duolite GT-73 resin (wet, 85%)	77	61	65	99.5	128	21
4	Duolite GT-73 resin (wet, 85%)	129	119	65	98.5	404	67

[a] **Note:** After oxidation with Oxone (8 mol %) and aqueous workup. Levels of Pd were measured directly in DMSO-diluted samples of crude solution using DCP-emission. [b] Isolated yield after crystallization from ethanol.

3. These byproducts mainly arise from the reaction of **2** with the unreacted **7** leading to **10** and **11** and the byproduct **14** arising from **13** of the first coupling step. Evidently, **14** was formed in the first coupling reaction from **8** by a subsequent Heck reaction and was not detected at that stage. Compound **14** was identified by HPLC/MS ($M^+ = 538$) as well as ^{1}H NMR after isolation from the crude reaction mixture by chromatography.



Palladium Removal during Workup

The last point that needed to be addressed in this double coupling step was the wide variation of the Pd and P levels in the isolated **3**. Variation in phosphine levels caused variable exotherms in the hydrogenation step, and the unpredictable Pd levels hampered development of an efficient method for Pd removal. To deal with the phosphines, we attempted to use adsorptive removal after oxidation of triphenylphosphine to the corresponding oxide. GC/MS analysis indicated that, after the second coupling, about half of the phosphine added into the reaction was already oxidized to phosphine oxide, while the remainder was easily oxidized with Oxone. After filtration and aqueous workup, adsorption studies were conducted using an equilibration method, and phosphinoxide levels were analyzed semiquantitatively by GC (Table 3). The best results were obtained with Panther Creek Clay (PC Catalyst), a bentonite-type mineral.

Another set of experiments showed that Panther Creek Clay also reduced palladium levels in toluene solutions of **3** by 60% (Table 4).

These results indicated that by the use of adsorption on Panther Creek Clay the level of phosphines could be lowered to 21 ppm in the crystallized product. However, Pd levels in the crystallized **3** were not meaningfully affected, even when Duolite GT-73 resin (containing thiol groups) was used in addition to the bentonite. Systematic experiments were therefore conducted to study the removal of Pd from non-oxidized and oxidized crude product solutions in toluene by adsorption and extraction. Levels of Pd were measured directly in DMSO-diluted samples of a solution of **3** using DCP emission (Table 5). While a reduction in Pd was

Table 5. **The effect of adsorbents on Pd-levels in toluene solution**

entry	adsorbent(s)	amount [% w/w][a]	contact time [h]	palladium in solution [ppm][b]
1	–		0	135
2	Panther Creek Clay	50	8	125
3	silica 60 Å	70	6	78
	Duolite GT73 wet	70		
	Na_2SO_4	180		
4	Duolite GT73 wet	70	6	107
	Na_2SO_4	180		
5	Duolite GT73 dried	33	24	88

[a] Of estimated product amount. [b] Determined using DCP-emission of toluene solutions in DMSO.

achieved with some adsorbents and combinations of adsorbents, the residual amount of Pd was still very high compared to our target of ≤4 ppm after hydrogenation. In this case, only 50 wt % of Panther Creek Clay was used to minimize loss of yield; however, Pd levels did not decrease as much as previously observed.

Distillation was found to be an interesting option for Pd removal. Thus, distillation in a Kugelrohr apparatus (0.2 mbar, 250 °C in the oven) gave pure **3** (99.75%, HPLC, area normalization) with Pd < 3 ppm. Similarly, this approach was successful with **1**, which has a lower boiling point (150−170 °C at 0.2 mbar) compared to **3**. However, this approach was considered not practical because of the high distillation temperature.

A better result came after we reversed our strategy. While our previous attempts had been directed at the *removal of palladium* from the reaction mixture, the new idea was to *remove the product* from the reaction mixture while ensuring that the palladium stayed in the solution with other impurities. Our intention was to crystallize **3** in the presence of a scavenging agent that kept the palladium in solution. To this end, a range of amines and S-containing compounds was screened (Table 6). The results with thiourea and *N*-acetylcysteine were very encouraging. Thiourea was included in the screening because Deloxan (sold by Degussa and recently discontinued), a resin known for its ability to adsorb palladium, contains *N*,*N*-disubstituted thiourea. A concentrated aqueous solution of *N*-acetylcysteine had previously been used to extract palladium out of organic solutions.[13a] Recently a salt formation followed by conversion to free base was reported by Manley and Acemoglu[13b] and others[13c] for reducing Pd to the desired specifications.

A detailed investigation of the influence of the water content of the crystallization medium revealed that increasing

Table 6. **Crystallization[a] of 3 from crude extracts: effect of additives on Pd level**

entry	additive [w/w of solution]	Pd [ppm]	P [ppm]	purity (peak area normalization) [%]	yield [%]
1	–	398	64	96.95	69.7
2	ethanolamine (1.3%)	68	11	96.86	70.1
3	maleic acid (1.3%)	216	19	97.82	47.5
4	TMEDA (1.0%)	100	16	97.04	69.7
5	triethanolamine (2.3%)	194	35	97.10	69.5
6	TRIS (1.5%)	72	17	96.7	71.7
7	**thiourea (1.0%)**	**20**	**5**	**97.35; S < 0.02%**	**70.5**
8	***N*-acetylcysteine (1.1%)**	**17**	**4**	**97.50; S < 0.05%**	**69.5**

[a] Crystallizations were performed by dissolving in ethanol, cooling to 47−43 °C, at which point a thick slurry formed, reheating to 55 °C, and slow cooling to room temperature, followed by stirring for 10−16 h.

Table 7. **Crystallization of 3 in ethanol from crude extracts: the effect of thiourea and water addition[a]**

entry	ethanol/water ratio [w/w]	thiourea [% w/w of solution]	appearance	Pd [ppm]	P [ppm]	purity (area normalization), [%]	yield [%]
1	100:0	0	tan	521	83	n.d.	73.3
2	100:0	1	yellow	30	8	98.66	73.1
3	90:10	0	tan	259	36	n.d.	70.3
4	90:10	1	yellow	24	5	n.d.	71.0
5[b]	90:10	1	yellow	22	<5	98.5	75.4[b]
6	90:10	2	yellow	16	<5	n.d.	71[c]
7	80:20	1	yellow	15	<5	98.5	71.2

[a] **Note:** Sulfur analysis shows S < 0.02%. These results were obtained from a single run with $Pd(PPh_3)_4$. [b] Cooled to 0 °C before filtration. [c] Corrected for small handling losses.

amounts of water decreased the Pd content of the product. The data, obtained from a reaction after aqueous workup, but without oxidative workup, are shown in Table 7.

From the above data it is clear that we had a method in our hands to crystallize **3** from Pd without any additional operations. Oxidative workup appeared unnecessary when crystallizing in the presence of thiourea or *N*-acetylcysteine. As thiourea is a suspected carcinogen, *N*-acetylcysteine was adopted as a choice additive.

Scale-Up in a LabMax: Back to Oxidative Workup

With most of the pieces of the process puzzle in hand, we commenced to perform the process in a Mettler LabMax reactor. Leak rates of vessels were tested in the lab by checking the change of pressure in evacuated reactor trains. The leak rate was in the range of 0.08 lb/h at 100 mbar, which is only 1% of the leak rate for which the pilot-plant vessels are certified (8 lb/h). Therefore, as a precaution, the bottom outlet pipe in the plant was kept under nitrogen, to avoid air being drawn into the reactor through the solution during vacuum operation.

Initial problems were encountered when the product **3** from the LabMax contained high Pd (120 ppm) and Cu levels (30 ppm). Precipitation of black material was observed on the hot glass surface during distillation and crystallization. When the reaction was repeated twice, Pd levels of 19 and 700 ppm were found. One of the major differences between these runs was that during the second run (19 ppm Pd) the crude reaction extract was held at ambient atmosphere for 4 days before solvent switch and crystallization, while the first run (120 ppm Pd) was held for 36 h, and in the third run (700 ppm Pd) the holding time was only 18 h, under nitrogen. Thus, we concluded that the reason for the high levels of Pd observed was the decomposition of the $Pd(0)/PPh_3$ complex (still present in the solution during the solvent switch and crystallization) to metallic, insoluble Pd. To alleviate the problem, the aqueous phase of the crude reaction mixture after the second coupling was drained, and the organic layer was subjected to oxidation by stirring in the air for 16 h at room temperature. After crystallization in the presence of *N*-acetylcysteine, a Pd level of 11 ppm was obtained. Safety considerations (air cannot be used in the plant) compelled us to compare the use of synthetic gas mixture of 5% O_2 in N_2 with hydrogen peroxide (3% solution, w/w) for this oxidation. The oxygen consumption of a reaction mixture in a 2000-mL stirred pressure vessel is depicted in Figure 3. The oxidation with 5% O_2 in N_2 required four exchanges of the headspace (volume ratio headspace:solution = 1:1) until the oxygen uptake minimized. On the other hand, during oxidation with 3% hydrogen peroxide (10 mol % vs **2**), an addition-controlled exotherm was observed ($\Delta T_{ad} \approx 5$ °C), and only a very weak exotherm remained for a brief period after the end of the addition. Peroxide levels were checked at intervals after the addition, and only single-digit ppm values of peroxide were found 4 h after the addition, mainly in the aqueous phase.

(13) (a) Villa, M.; Cannata, V.; Rosi, A.; Allegrini, P. (Zambon Group S. P. A.). WO98/51646, 1998. (b) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436. (c) Chen, C.-Y.; Dagneau, P.; Grabowski, J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. *J. Org. Chem.* **2003**, *68*, 2633. (d) Urawa, Y.; Miyazawa, M.; Ozeki, N.; Ogura, K. *Org. Process Res. Dev.* **2003**, *7*, 191.

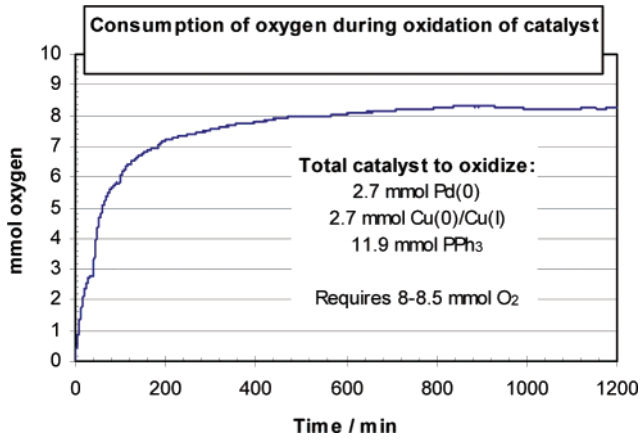


Figure 3. **O_2 consumption during oxidation with 5% O_2 in N_2, calculated from headspace pressure data.**

After washing the organic layer with sodium bisulfite solution and brine, samples of the solution were concentrated to dryness and submitted for safety testing. A decomposition exotherm (≥60 kJ/kg) with an onset around 120 °C was found with the RADEX calorimeter for both oxidized samples. The size of the exotherm was proportional to the amount of oxidant used: 30 mol % of hydrogen peroxide afforded an exotherm about 3 times larger (≥160 kJ/kg). Isoperibolic calorimetry did not reveal any exotherm at 100 °C. As a result of the above studies, the new workup was conducted as follows: The reaction mixture was cooled, the aqueous phase was removed, and the remaining mixture was oxidized with hydrogen peroxide (3%, 0.1 equiv vs **2**), filtered, and washed with sodium bisulfite solution and brine. After solvent switch to ethanol, **3** was crystallized from ethanol/water 80/20 (w/w) in the presence of 1.3% (w/w of solution) of *N*-acetylcysteine.

The Drug Substance Step

The conversion of **3** to **1** involved a controlled catalytic hydrogenation of acetylenic system to an ethane derivative with the intermediacy of the major *cis*- and the minor *trans*-olefins. This process is complicated by the fact that the desired **1** can undergo further hydrogenation.

Figure 4 shows a typical hydrogenation progress as monitored by HPLC. At the beginning of the reaction, **3** was hydrogenated to a *cis*-olefin and a small amount of *trans*-olefin. This olefinic mixture was then further hydrogenated to **1**. The *trans*-olefin, although a minor intermediate, hydrogenated very slowly compared to *cis*-olefin and survived till the end. As hydrogenation was continued to reduce the *trans*-olefin to a specified limit, the over-hydrogenation of **1** started interfering.

As 2-propanol was found to be the best solvent for the recrystallization of **1**, hydrogenation was studied in great detail with 10 wt % of **3** in ^{i}PrOH and 8.3% of catalyst by weight of **3**. Under these conditions, most of **3** remained undissolved initially. However, as the hydrogenation progressed and by the time the hydrogen consumption leveled off, all of **3** went into solution.

For the recrystallization of **1** a 50% (v:v) of 2-propanol/water solution was selected on the basis of solubility. The optimized ratio of **1** to solvent (50% 2-propanol/water) was found to be 1 g/4.5 mL. Utilizing these conditions and in the presence of *N*-acetyl-L-cysteine, the drug substance was isolated with acceptable palladium levels of <4 ppm (Table 8) in a reproducible manner. No *N*-acetyl-L-cysteine was detected in the isolated **1**.

Table 8. **Removal of palladium from 1 using *N*-acetyl-L-cysteine[a]**

			Pd in **1**	
entry	Pd in **3**, ppm	concentration of cysteine (g/mL)	before crystallization, ppm	after crystallization, ppm
1	17	–	10	6
2	17	0.5%	10	1
3	120	1.0%	21	<1
4		0.5%		<2
5	30	0.5%	11	<2

[a] The solvent for crystallization: 50% 2-propanol/water; concentration: C7/solvent = 1 g/4.5 mL. All samples were analyzed by Robertson Microlit Lab.

Compound **1** was found to exist in two polymorphic forms with mp of 76.7 °C for form A and mp of 75.6 °C for form B. Form A was the preferred polymorphic form from the preparation point of view. It was readily prepared by cooling the hot saturated solution of **1** to 25 ± 2 °C followed by seeding with form A crystals and cooling to 0 ± 2 °C at 1 deg/min. After 2 h, the solids were filtered, washed with water, and dried to give form A. Depending on the scale, when 2-propanol/water was used as a wash solvent, the isolated **1** was found to transform partly to form B during the drying process. When water as the last wash solvent, no transformation of form A to form B was observed even in plant batches. Polymorphic form B was prepared from the saturated solution of **1** in 50% 2-propanol/water at 35 °C with form B seeds. The crystals that formed at this stage were a mixture of form B and form A in the ratio of 70:30. Stirring this mixture over 5 days at room temperature generally gave pure form B.

Conclusions

In conclusion, we have developed an efficient, large-scale, chromatography-free synthesis of **1** using palladium-catalyzed Sonogashira cross-coupling as the key step for making the unsymmetrical ethyne **3**. A novel approach for removing residual palladium was utilized in which an additive retained the palladium in the mother liquor in soluble form.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument; coupling constants *J* are given in hertz. Compound **6** was obtained from Alfa, **7** and other reagents were from Aldrich, and compound **2** was made internally using the our published method.[14] HPLC analysis of **3** and **1** was performed on a Symmetry C18, (5 μm, 3.9 mm × 150 mm) column at

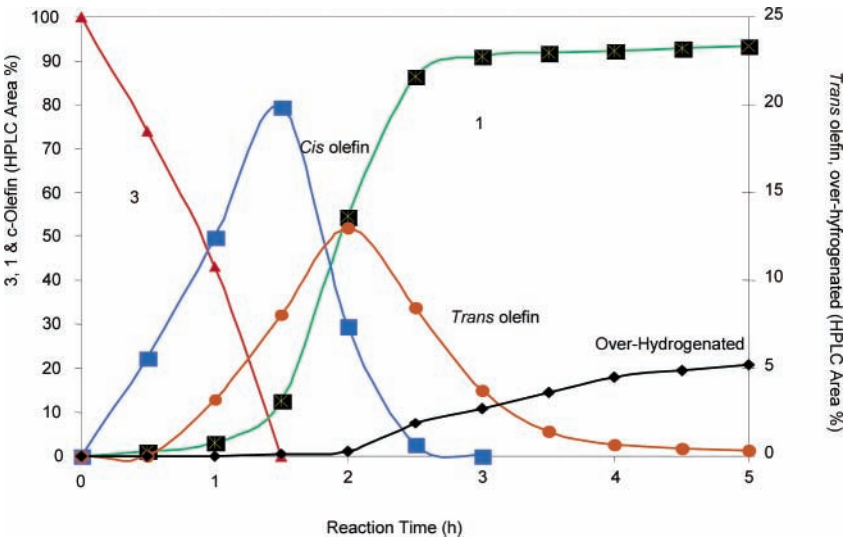


Figure 4. **Area percent of 1, intermediate *cis*- and *trans*-olefins, and over-hydrogenated byproduct versus reaction time.**

40 °C with mobile phases A [25 mM NH_4OAc buffer: methanol:water = 10:50:40 v/v/v] and B [25 mM NH_4OAc buffer:methanol = 10:90 v/v] at a flow rate 1 mL/min. A gradient from 50% A/50% B (0 min) to 0% A/100% B (8 min) to 50% A/50% B (25 min) was used. Sample preparation: 15−25 μL of sample filtrate + 1.5 mL of methanol + 0.5 mL of water; injection: 50 μL of sample solution; detector: UV/vis @ 268 nm; retention times: **1** = 7.15 min; **3** = 7.53 min; *cis*-olefin: 6.65 min; *trans*-olefin: 8.38 min; over-hydrogenated product: 3.15 min. For the (**6** + **7**)-to-**8** conversion, an HP5890 GC with an HP5 column (30 m/0.25 mm, film thickness 0.25 μm), temperature program set at 100 °C (3 min, heating rate 20 °C/min) to 250 °C (17.5 min) an injector temperature of 220 °C with helium as carrier gas, and an FID detector (260 °C) was used. Response factors and retention times are **6**: 1.661, 8.27 min; **7**: 2.612, 2.18 min; **8**: 1.0, 10.02 min; diisopropylamine: 2.612, 2.18 min; and triphenylphosphine: 12.70 min. HPLC analysis of **2** + **8** to **3** was performed on a Symmetry C18, (5 μm, 4.6 mm × 150 mm) column with mobile phases A (acetonitrile) and B (0.01 mol/L $(NH_4)_2SO_4$ in water at a flow rate of 1 mL/min. A gradient from 50% A/50% B (0 min) to 50% A/50% B (5 min) to 90% A/10% B (25 min) was used. Sample preparation: 200 μL of sample in 50 mL of acetonitrile; injection: 5 μL of sample solution; detector: UV/vis @ 230 nm; retention times: **2** = 6.45 min, **8** = 3.98 min, and **3** = 9.96 min.

6-[2-(2,5-Dimethoxyphenyl)ethynyl]-4-ethylquinazoline (3). *Degassing procedure.* Heat the mixture to reflux and hold for 30 min, while continuously sweeping the headspace of the vessel with nitrogen to flush away oxygen. Cool to room temperature. Once the Pd^0 catalyst is formed, it becomes oxygen sensitive. To avoid oxidation of the catalyst and of copper(I), the reaction substrates and solvents must be degassed prior to charging the 2-methyl-3-butyn-2-ol (**7**) and heating. The reaction must be carried out under nitrogen atmosphere in a vacuum- and gas-tight vessel. A leak test of the vessel should be performed. Leaks in the bottom valve of the vessel are especially detrimental. It is recommended to keep the bottom outlet tube under nitrogen during the vacuum distillations between the coupling reactions.

Charge a 3-L, four-necked round-bottomed flask with toluene (900 mL), 2-bromo-1,4-dimethoxybenzene (**6**, 117.3 g), and diisopropylamine (165 g), and degas the mixture. Charge a 2-L LabMax reactor with bis(triphenylphosphine)-palladium dichloride (3.79 g) copper(I) iodide (1.026 g) and triphenylphosphine (3.39 g). Inertize by evacuating and venting the vessel with nitrogen. Repeat two more times. Start stirring, and transfer the contents of the round-bottomed flask into the 2-L reactor. After stirring for 30 min at 25 ± 3 °C, charge 2-methyl-3-butyn-2-ol (**7**, 68.1 g) and heat the contents of the vessel to 78 ± 2 °C. Stir at this temperature for 13 h. Cool the reaction mixture to 25 ± 5 °C. Stir rapidly, evacuate the reactor to 50−100 mbar, and heat slowly to distill off solvent, concentrating the mixture to 500−600 mL (42% ± 5% of the original volume). In a 3-L round-bottomed flask, degas toluene (600 mL), and transfer to the distillation vessel. Continue to distill at 50−100 mbar, stirring rapidly and concentrating the mixture to 500−600 mL (42% ± 5% of the original volume). Sample and check for residual **7**. Charge a 3-L four-necked round-bottomed flask with 6-bromo-4-ethylquinazoline (**2**) (113.5 g), tetrabutylammonium bromide (5.70 g), toluene (600 mL), and water (360 mL). Degas the biphasic mixture and hold under nitrogen. After concentrating the reaction mixture in the LabMax reactor to the desired volume, lower the jacket temperature, cut off the vacuum, bring to atmospheric pressure with nitrogen, cool below 40 °C, and charge the solution of **2** into the reactor. Add 50% sodium hydroxide solution (150 g) and heat the mixture under vigorous stirring at reflux for 3 h. Sample after 3 h and analyze for remaining **2**. If **2** remains, continue and sample again 1 h after the previous sampling. Continue until less than 0.5 area % **2** (vs product) remains. Cool the reaction to 40 °C. Switch off stirring and remove the bottom layer after settling of the layers. Cut the layers so that the black metal particles at the interface remain with the organic (top) layer. Add toluene (400 mL), cool to 25 ± 3 °C, and

(14) Prasad, K.; Lee, G. T.; Chaudhary, A.; Girgis, M. J.; Streemke, J. W.; Repič, O. *Org. Process Res. Dev.* **2003**, *7*, 723.

add a solution of hydrogen peroxide 30% (6.6 g) in water (60 mL) over 15 min. Stir for 4 h at 25 ± 3 °C and filter through a 1.2-cm thick pad of Celite Hyflo (19.7 g). Rinse the reactor with toluene (100 mL) and wash the filter cake with the rinse. Combine with the filtrate. Transfer the filtrate to a 3-L separatory funnel and remove the bottom, aqueous layer. Add a solution of sodium chloride (137.5 g) and sodium bisulfite (9.53 g) in water (402 g), and stir for 15 min. Cut the phases carefully, so that any rag layer remains with the aqueous layer. Transfer the organic layer from the separatory funnel to the cleaned 2-L LabMax reactor, equipped for vacuum distillation. Stir rapidly and concentrate the solution to a minimum volume at 50−100 mbar. When the product crystallizes to form a thick slurry, lower the jacket temperature to 30 °C, cut the vacuum, vent with nitrogen, and add ethanol (850 mL). Heat to 65−70 °C (T_J < 80 °C) to dissolve the product, cool to 30 °C, stir rapidly, and concentrate to a minimum volume under vacuum. Add ethanol (350 mL) to a known volume marker in the vessel (in this case 810 mL). Add about 250 mL of ethanol and heat to reflux to dissolve any material obscuring visibility of the marker, if necessary. Sample the slurry and analyze for the toluene/ethanol ratio. If the concentration of toluene is <2 mol %, bring to a volume of 900 mL by addition of ethanol (90 mL). Heat the mixture (T_J < 80 °C) under nitrogen to dissolve everything and add a solution of *N*-acetylcysteine (11.7 g) in water (150 g). Stir for 10 min at T_J = 75 °C. Cool to 45 ± 5 °C to initiate crystallization. After crystallization starts, stir for 15 min at 45 ± 2 °C, reheat to 55 ± 2 °C over 20 min, hold for 20 min, then cool at approximately 0.33 °C/min to 20 °C. Stir for no less than 4 h at this temperature. Filter the crystals, rinse the reactor with ethanol/water (80:20, w/w) (80 mL) and wash the filter cake with the rinse. Wash the crystals with fresh ethanol/water (80:20, w/w) (200 mL) and dry in a vacuum oven at 50 °C and <150 mbar vacuum for 15 h, Yield: 114.0 g (74.8% based on **2**); Pd = 7 ppm; Cu < 1 ppm; P = 6 ppm; S < 0.005%; chemical purity 99.26%; mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, J = 7.5 Hz, Me); 3.34 (2H, q, J = 7.5 Hz, CH_2); 3.82 (3H, s, CH_3); 3.92 (3H, s, CH_3); 6.86−6.95 (2H, m, phenyl ring); 7.11 (1H, d, J = 2.83 Hz; phenyl ring); 8.01 (2H, s, quinazoline ring) 8.33 (1H, s, quinazoline ring); 9.22 (1H, s, quinazoline ring, N═C<u>H</u>−N); ^{13}C NMR (300 MHz), δ in $CDCl_3$: 13.03, 28.09, 56.23, 56.83, 88.21, 92.77, 112.41, 112.47, 116.83, 118.57, 123.26, 123.97, 128.10, 129.61, 136.64, 149.59, 153.65, 155.01, 155.46, 172.55 ppm.

6-[2-(2,5-Dimethoxyphenyl)ethyl]-4-ethylquinazoline (1). Charge a slurry of 4.17 g of 10% palladium on carbon (50% H_2O, w/w) in 25 mL of 2-propanol. Add a slurry of 50.0 g of 6-[2-(2,5-dimethoxyphenyl)ethynyl]-4-ethylquinazoline (**3**) in 150 mL of 2-propanol to a 1-L RC1 MP10 medium pressure reactor vessel through a funnel with an addition tubing. Use an additional amount of 325 mL of 2-propanol in portions to complete the transfer of the slurry. Seal the reactor. Start agitation and slowly increase the speed to 300 rpm. Purge the reactor with nitrogen at 40 psig five times. Stop the stirring and depressurize the reactor. Pressurize the reactor with hydrogen at 40 psig and depressurize. Repeat this process four times. Keep constant hydrogen pressure in the reactor at 40 psig. Start stirring after hydrogen is consumed and reactor/jacket temperatures reach constant levels, take samples at 1 h intervals, and analyze by HPLC. When the process steering control data indicate that the reaction mixture contains <0.7 area % of *trans*-olefin, stop agitation and close the hydrogen supply valve to terminate the reaction. Depressurize the reactor and repressurize the reactor with nitrogen and depressurize. Transfer the reaction mixture to an Erlenmeyer flask. Wash the reactor with 2 × 100 mL of 2-propanol. Filter the reaction mixture through the Hyflo Supercel pad. Rinse the container and wash the filter cake. Combine the filtrates and transfer to a 1-L LabMax reactor. Concentrate the filtrate at a jacket temperature of 50 ± 5 °C under 95−105 mbar. Carefully control the solution level to a premarked level of 158 mL. Take a sample for process steering control. If the analytical data show that ^{i}PrOH/**1** is out of the desired range of 2.1−2.4 mL/g, adjust 2-propanol level to 2.25 mL/g of **1** either by adding or by distilling off, depending on the result. If ^{i}PrOH/**1** ratio is in the range, the amount of 2-propanol need not be adjusted and go to next step. Dissolve 2.25 g of *N*-acetyl-L-cysteine in 113 mL of water and add the aqueous solution to the reactor. Stir and heat gently to reflux to obtain a clear yellow solution. Cool to 25 ± 2 °C and seed with 0.03 g of **1** (crystalline form A), hold at the same temperature for 0.5 h, then cool to 0−3 °C at a rate of 1 °C/min, and hold for 2 h. Filter, wash the reactor and crystals with 80 mL of an ice-cooled 2-propanol/water (1/1 v/v), and wash the filter cake with 20 mL of an ice-cooled 2-propanol/water (1:1 v/v). Wash the filter cake with 100 mL of water. Dry the product at 50 °C (60−80 mm) until LOD reaches <1% (in this case 18 h) to obtain 39.5 g (78% yield) of **1**, mp 76.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.5 Hz); 2.96−3.10 (2H, m, CH_2); 3.08−3.10 (2H, m, CH_2) 3.25 (2H, q, J = 7.5 Hz, CH_2); 3.69 (3H, s, CH_3); 3.74, (3H, s, CH_3); 6.64−6.79 (3H, m, phenyl ring); 7.71−7.78 (2H, m, quinazoline ring); 7.95 (1H, d, J = 8.5 Hz, quinazoline ring); 9.17 (1H, s, quinazoline ring, N═C<u>H</u>−N);^{13}C NMR (300 MHz, $CDCl_3$), δ 12.99, 28.00, 32.65, 36.76, 55.98, 56.16, 111.50, 111.60, 116.88, 123.36, 123.94, 129.17, 130.81, 135.50, 142.11, 148.93, 152.07, 153.75, 154.45, 172.05 ppm.

Acknowledgment

We are indebted to Dr. Helmut Boehnke and Mr. Christoph Ziltener for helpful discussions, to Dr. Apurva Chaudhary of our reaction engineering lab for calorimetric data and k_L measurements, to Dr. Tao He for LC/MS, Ms. Jyoti Patel and Dr. Steve Fazio for analytical support, Dr. Paul Sutton and his group for DSC measurements and solubility study data. The development of these steps was supported by Mr. Paul Lee, our plant engineer, and by Mr. Robert Duval, the head of the Thermal Safety Lab. Special thanks to Dr. Ching-Pong Mak for suggesting distillation as a possibility for removing the residual palladium.

Received for review June 11, 2003.

OP034072X