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Evaluation of Kilogram-Scale Sonagashira, Suzuki, and Heck Coupling Routes to Oncology Candidate CP-724,714

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Abstract:

The synthesis of the anti-cancer compound 2-methoxy-*N*-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)phenylamino]quinazolin-6-yl}-*E*-allyl)acetamide (CP-724,714) (1) on multikilogram scale using several different synthetic routes is described. Application of the Sonogashira, Suzuki, and Heck couplings to this synthesis was investigated to identify a safe, environmentally friendly, and robust process for the production of this drug candidate. A convergent and selective synthesis of the candidate was identified which utilizes a Heck coupling of a protected allylamine to install the critical olefin.

CP-724,714 (**1**) is a selective ErbB2 angiogenesis inhibitor currently being investigated for the treatment of breast, ovarian, and other types of cancer. Due to the large and rapid bulk requirements of the clinical program as well as some additional external factors, four synthetic routes to this candidate were run on multikilogram scale. This unusual history allowed for a comparison of some of the more common palladium coupling reactions and their application on large scale. All routes investigated utilized a common retrosynthetic disconnection across the aryl−olefin bond, utilizing different palladium-catalyzed cross couplings for assembly (Scheme 1).

Sonogashira Coupling Route. The original Discovery synthesis of CP-724,714 employing a Sonogashira coupling and Red-Al reduction to introduce the *trans*-olefin side chain is depicted in Scheme 2.

This route, with some minor modifications, was used to produce 1.3 kg of **1**. Sonagashira coupling of 6-iodo-4-chloroquinazoline[1] (**7**) with BOC-protected propargylamine[2,3] (**8**) proceeded smoothly at room temperature to produce acetylene **9** on 5.7 kg scale. The reaction was exothermic, and the rate of heat generation was controlled by lowering the copper and palladium catalyst levels. The reaction mixture was treated with activated carbon (KBB Darco) in hot ethyl acetate to lower the amount of residual palladium in the product. The ethyl acetate was replaced by 1:1 dichloroethane/THF, and 1 equiv of aniline **4**[4] was added based on the amount of acetylene **9** calculated from a quantitative HPLC potency assay. The product obtained after heating was isolated as a crystalline solid from ethyl acetate. Assay by inductively coupled plasma mass spectroscopy (ICPMS) indicated less than 50 ppm of copper and palladium in the material at this stage in the synthesis. The residual metal levels continued to decline throughout the synthesis and were well below 20 ppm in the active pharmaceutical ingredient (API). Compound **10** was recovered in 73% yield over the two steps (3.5 kg scale).

Reduction of acetylene **10** with Red-Al proved to be technically challenging. The reaction is sensitive to reaction time, temperature, and stoichiometry. Over-reduction of the acetylene and incomplete reaction both proved to be issues, and the resultant impurities (unreacted starting material and alkane) were difficult to purge from the relatively insoluble drug substance. The reaction was optimally run using 2.8 equiv of Red-Al at −5 to 0 °C. Fewer impurities were generated when the acetylene was added to the Red-Al (vs the reverse order). Compound **10** was not soluble in THF at the reaction temperature and had to be transferred to the Red-Al as a slurry. This transformation was accomplished on 1.75 kg scale and provided material containing 3% unreacted **10** and 3% overreduced alkane, comparable to our best lab-scale results. Deprotection of the BOC group was effected in THF with aqueous HCl, resulting in the precipitation of the bis-hydrochloride as an easily handled solid in 83% yield for the two steps. Amide formation using excess triethylamine to free-base the HCl salt and methoxyacetyl chloride in place of methoxyacetic acid/carbonyldiimidazole produced amide **1**. Two recrystallizations to lower the levels of the acetylene and alkane impurities were required (ethyl acetate followed by acetonitrile) and provided a disappointing 38% yield for the amide formation and purifications. It is noteworthy that the crystal form of **1** which precipitated from the ethyl acetate recrystallization was less soluble than the original form and could not be redissolved in a workable volume of ethyl acetate (<30 L/kg). This necessitated the switch to aceto-

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(1) Prepared in 75% by published methods from iodoanthranillic acid (**5**): (a) Edincott, M. M.; Alden, B. W.; Sherrell, M. L. *J. Am. Chem. Soc.* **1946**, *68*, 1303. (b) Hudson, A. T.; Vile, S.; Barraclough, P.; Franzmann, K. W.; McKeown, S. C.; Page, M. J. World Patent WO9609294, 1996.

(2) Prepared from propargylamine and BOC anhydride in methylene chloride at 0 °C. The material is a low-melting solid (MP = ∼25−30 °C) and was handled as a melt. Spectral data was consistent with that reported in the literature (ref 6).

(3) Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727.

(4) Prepared by S_NAr reaction between 3-hydroxy-6-methylpyridine (**3**) and 2-chloro-5-nitrotoluene (**2**) (K_2CO_3, DMF, 110 °C) followed by hydrogenation to the aniline (10% Pd/C, H_2, methanol, water).

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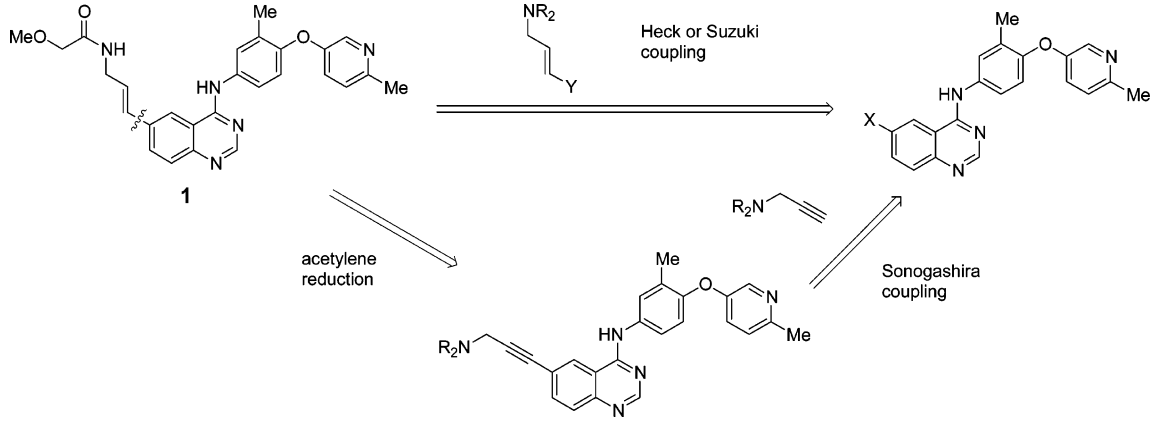
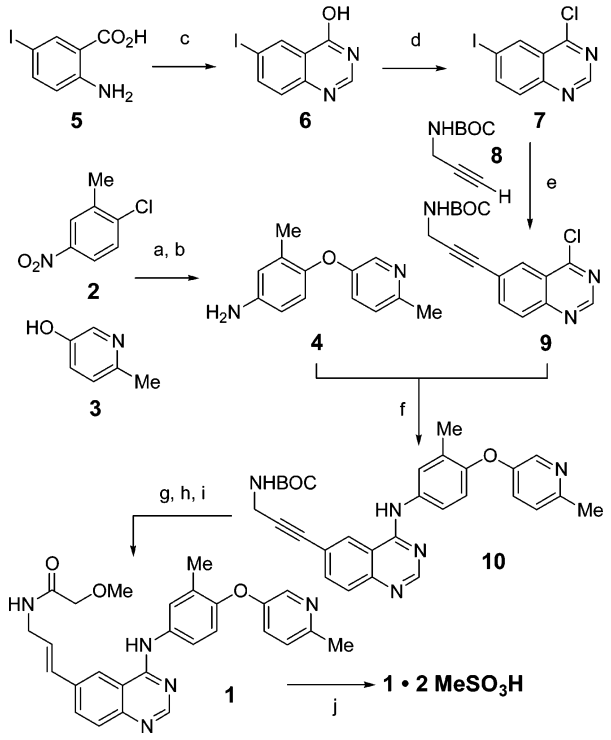
Scheme 1. **Retrosynthesis of CP-724,714**



Scheme 2. **Discovery synthesis of CP-724,714**[a]



[a] Process conditions and results: a) K_2CO_3, DMF, 110 °C; b) 10% Pd/C, H_2, MeOH, H_2O, 62%, 2 steps; c) formamidine acetate, EtOH, reflux, 80%; d) $(COCl)_2$, DMF, DCE, 53%; e) $Pd(PPh_3)_2Cl_2$; CuI, *i*-Pr_2NH, THF, 65 °C, 18 h; f) DCE/*t*-BuOH, 80 °C, 1 h, 73%, 2 steps; g) Red-Al; THF; 0 °C; 2 h; h) HCl, MeOH, 83%, 2 steps; i) i) $MeOCH_2CO_2H$, CDI, CH_2Cl_2, 93%; ii) EtOAc; iii) MeCN, 38%; j) $MeSO_3H$, ^{i}PrOH. 93%.

nitrile for the second purification. Finally, dimesylate salt formation was accomplished in 2-propanol in 93% yield to complete the preparation of 1.3 kg of the API salt.

From a bulk-preparation perspective the route was operable; however, there was room for improvement. Enolization of the α-methoxyacetamide under the Red-Al reduction conditions necessitated the protection of the amine as its BOC carbamate, followed by late-stage deprotection and amide formation. In addition to the required protection and deprotection steps, the Red-Al reduction of **10** proved to be difficult to execute on large scale, with over-reduction and incomplete reaction evident under all conditions investigated and the quench being highly time-sensitive. The over-reduced alkane and the unreduced acetylene proved difficult impurities to purge and exacted a significant yield penalty during the purification.

From a worker-safety perspective, we also learned some important lessons. 6-Iodo-4-chloroquinazoline **7** tested positive for sensitization in the LLNA[5] test and was also found to be an eye irritant. CP-724,714 was also found to be positive as a sensitizer in the LLNA test. These results affected our strategy with regard to regulatory starting material selection as well as what equipment is selected to process material through the chemistry developed.

Additionally, the solubility of CP-724,714 was characterized. The drug has a low solubility in most organic solvents such as ethyl acetate and acetonitrile but is soluble in THF, ethyl acetate with 10% THF, wet ethyl acetate, and wet 2-methyltetrahydrofuran (MTHF). While some purification of the API could be achieved at the free-base stage (vide infra), recrystallization of the dimesylate salt failed to afford any enrichment of the desired product.

Shortly after the 1.3 kg batch was produced, the dimesylate salt was found to be unstable. The salt was hygroscopic and delequesced under humid conditions (>75% humidity). Under acidic conditions in protic media, solvolysis of the quinazoline−aniline bond to yield hydroxyquinazoline **12** and aniline **4** proved quite facile (Figure 1). This decomposition provided warning against handling API or intermediates bearing the 4-aminoquinazoline functionality in highly acidic media. A number of salts, polymorphs, and crystal forms of the API were screened, and the sesquisuccinate (1.5×) salt was selected to progress in the drug trials after extensive stability and bioavailability testing.

A search for a new route to the drug substance was undertaken with the goals of increased convergency, improved selectivity of the olefin installation, a minimal level of worker safety issues, high purity, minimized raw material costs, and minimized environmental impact. Several alternatives to the Sonagashira coupling route were considered including aldol condensation of a 6-aldehydoquinazoline with an amide enolate or a late-stage Pd-catalyzed coupling of the 6-haloquinazoline **13** with an appropriately functionalized allylamine such as **14** or **15** (Scheme 3). We chose to focus on Pd-catalyzed reactions to install the olefin as the 6-

(5) The LLNA (local lymph node assay) is an indicator as to whether a compound is a sensitizer.

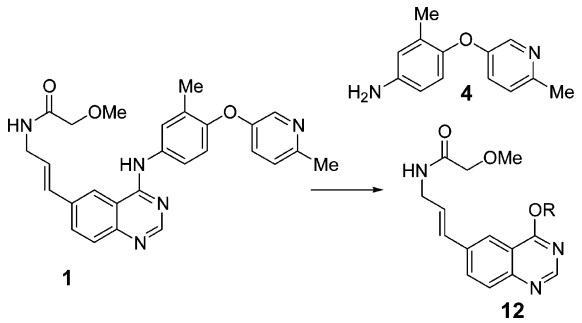
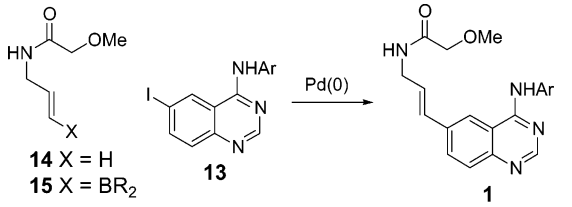


Figure 1. **Decomposition of CP-724,714 under acidic, protic conditions.**

Scheme 3. **Potential routes involving palladium couplings to provide CP-724,714 directly**



haloquinazolines proved more inexpensive and stable than the aldehyde counterparts. Most attractive of the Pd-catalyzed routes would be a Heck coupling,[6,7] as it would require a less expensive and less functionalized coupling partner. As a fall-back position, Suzuki coupling[8,9] of *trans*-vinylborane **15** derived from hydroboration of the acetylene would provide a rapid route to the candidate using the same starting materials as the first synthesis.

Suzuki Coupling Route. Immediate bulk requirements drove the decision to investigate the Suzuki coupling first, as it was considered less likely to pose problems with regard to olefin geometry and substitution pattern than would a Heck coupling.

Functionalized iodoquinazoline **13** was prepared by heating 6-iodo-4-chloroquinazoline (**7**) with aniline **4** in 2-propanol (Scheme 4). Product **13** was isolated as the HCl salt by directly filtering the reaction mixture. Water or primary alcohol solvents in the reaction mixture led to the production of ethereal byproducts resulting from reaction of solvent with **7**. Using 2-propanol was the preferred process on scale as any 6-iodo-4-hydroxyquinazoline present in the starting material (**7**) was effectively purged, as compared to a number of other solvents in which the reaction could be run. In the course of running a bulk campaign, nine batches were run using as much as 50 kg of **7** with yields ranging from 91 to 97% and purity from 98.5 to 99%.

Acetylene **16** was prepared by reaction of propargylamine with methoxyacetyl chloride. The product was isolated in good purity as an oil after aqueous work-up, obviating the need for any additional purification. Differential scanning calorimetry data (DSC) on **16** indicated that distillation was not a safe option for the purification of this material.[10]

The hydroboration/Suzuki coupling sequence was carefully studied. Hydroboration of acetylene **16** required 2 equiv of disubstituted borane to proceed to completion:[11] the first to deprotonate the amide and the second to effect hydroboration. Isoamylborane, thexylborane, and 9-BBN all worked nicely to hydroborate **16**. Isoamylborane was excluded from consideration due to the low flash point of 2-methyl-2-butene (−45 °C), which precluded its use in our pilot plant. 9-BBN was selected over thexylborane as it is sold either as a stable solid or a prepared solution that can be easily handled. In addition, there is significant literature on the hydroboration of acetylenes using 9-BBN.[12] Concern about removing alkylborane by-products after the Suzuki coupling did lead us to investigate hydroborations using catecholborane or dialkoxyboranes such as pinacolborane; these reactions did not proceed to any useful extent, even in the presence of catalysts such as Wilkinson's[13] or boranes such as 9-BBN or dicyclohexylborane.[14]

The Suzuki coupling could be run using the hydroboration reaction mixture directly. The conditions initially investigated were $Pd(OAc)_2$, Ph_3P, K_2CO_3, H_2O, THF, 3 equiv of 9-BBN: 3 equiv of acetylene: 1 equiv of of iodide. The reaction was heated for 18 h and cooled, the water layer was separated, and the product was extracted into aqueous HCl and washed with ethyl acetate. The water layer was then basified, and the product was extracted into ethyl acetate and crystallized. Following this sequence, a 19% yield (following purification) for the hydroboration−Suzuki sequence was achieved on 30 kg scale. Significant optimization was required prior to proceeding further with this synthesis.

Improved conditions for the hydroboration of **16** were developed using 2 equiv of 9-BBN and 1 equiv of acetylene **16**; the subsequent Suzuki reaction proceeded with much higher purity than the reaction described above. Switching to $Pd_2(dba)_3$ (5 mol %), the reaction time was reduced to less than 6 h, and the phosphine ligand was not necessary, obviating the need for its removal at the end of the reaction.

(6) Reviews: (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3. (b) Bräse, S.; deMeijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Deiderich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) deMeijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(7) Heck reactions of aryl chlorides: (a) For an overview: Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (c) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481. (d) Beller, M.; Zapf, A. *Synlett* **1998**, 792. (e) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995. (f) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734. (g) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465. (h) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (i) Herrmann, W. A.; Elison, M.; Fischer J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371. (j) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357.

(8) (a) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Deiderich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (b) Miyamura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(9) Suzuki reactions of aryl chlorides: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(10) Decomposition with a release of >1000 J/g occurs ~228 °C.

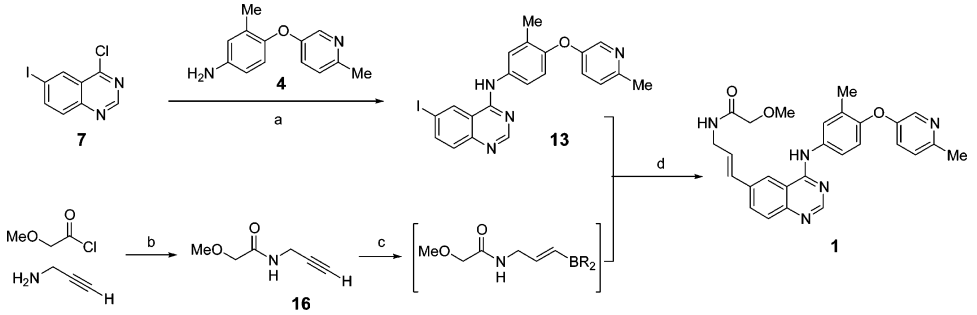
(11) If less than 2 equiv of hydroborating agent are employed in the acetylene hydroboration, a number of impurities are formed in the Suzuki coupling at higher levels (vide supra).

(12) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065.

(13) Anon. *Aldrichimica Acta* **1989**, *22*, 80.

(14) (a) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. b) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. *Synth. Commun.* **1995**, *25*, 1957.

Scheme 4. **Suzuki coupling route to CP-724,714**[a]



[a] Reagents and conditions: a) IPA, °C, 91−97%; b) MTHF, Et_3N; c) 9-BBN, THF, 30 °C; d) i) $Pd_2(dba)_3$, K_2CO_3, H_2O, THF; ii) H_3PO_4; iii) NaOH, 55%.

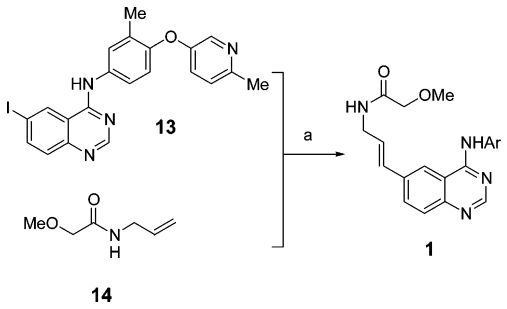
The shorter reaction time also reduced the isolated amount of primary amine resulting from amide hydrolysis. Due to concern about the stability of **1** in strongly acidic water,[15] phosphoric acid was substituted for HCl to extract **1** into water during the isolation. A greatly reduced rate of decomposition was observed in this aqueous system as compared to that in HCl. Methylene chloride was substituted for ethyl acetate as the organic solvent during the extractions to avoid acetamide formation from the primary amine impurity (described above) during the work-up. As a result of these changes, the isolated yield of desired product was increased by almost 3-fold from 19% using the conditions described above to ∼55% in lab-scale pilots using the improved conditions.

In practice, 9-BBN was used in solution in our pilot plant in the course of a 10-kg bulk run.[16] As the maximum concentration of 9-BBN commercially available was 0.5M,[17] 2 M borane−THF was procured to generate 9-BBN in situ for a planned 50 kg campaign. After prolonged storage at ambient temperature, and prior to any manipulation, one of the cylinders of borane−THF spontaneously underwent a BLEVE[18] in a large explosion that injured a number of our colleagues.[19]

The incident with 2 M borane−THF served to accelerate efforts to replace the Suzuki coupling with a Heck coupling. Provided the coupling could be run to give product in high purity, the Heck coupling would have a number of advantages over the Suzuki coupling including safety (handling of borane/alkylborane reagents, acetylene thermal stability issues), cost (no hydroborating agent required), ease of execution, and environmental and purity issues (no need to remove alkylborane side products).

First-Generation Heck Coupling Route. Initial attempts at utilizing a Heck coupling to make API were encouraging. The most aggressive strategy was investigated first, wherein allylamine methoxyacetamide **14**[20] would be coupled with quinazoline **13** to directly generate **1** (Scheme 5). Allylamide **14** (2 equiv) reacted with quinazoline **13** in the presence of $Pd(OAc)_2$, Ph_3P, and NaOAc in DMF to provide the desired product in ∼50% in situ yield as determined by HPLC

Scheme 5. **First-generation Heck coupling route to CP-724,714**[a]



[a] Reagents and conditions: a) $Pd_2(dba)_3$, IPA, Et3N, 78 °C, 56% in situ yield.

analysis. The reaction profile was quite messy with a number of impurities formed, one in greater than 30% yield. This particular impurity has the equivalent mass to **1** and was tentatively assigned as the 1,1-disubstituted olefin isomer. Extensive optimization revealed that selectivity for **1** vs other impurities, particularly the presumed 1,1,disubstituted olefin isomer, jumped when the reaction was run using triethylamine as solvent or cosolvent (e.g. with 2-propanol). $Pd_2(dba)_3$ without added phosphine was superior to $Pd(OAc)_2$ with Ph_3P or $(o\text{-tol})_3P$ in this reaction. Heating **13** and **14** in 10:1 2-propanol: triethylamine in the presence of 5 mol % $Pd_2(dba)_3$ for 2 h resulted in formation of **1** in >50% in situ yield and only 12% of the presumed 1,1-disubstituted olefin impurity. Low yields of the desired product could be obtained after crystallization from acetonitrile (<10%).

As 10 kg of material was required for clinical studies, a campaign utilizing the Heck chemistry was run which required bulk chromatography to purify the Heck coupling reaction mixture (as the recovery from crystallization was low). The allylamine methoxyacetamide was produced in 2-methyltetrahydrofuran (MTHF) with allylamine, triethylamine, and methoxyacetyl chloride at 25 °C. After acid and base washes, the organic layer was dried via an azeotropic distillation with MTHF until a water level of 0.5% was achieved, followed by solvent removal to leave an oil suitably pure for use in the Heck coupling.

Two batches were run through the Heck coupling using the conditions described above on 15-kg scale, resulting in identical in situ yields to those of the laboratory pilots. The bulk reactions were filtered through Celite and concentrated to the lowest stirrable volume, and the remaining solvent was replaced via co-distillation with THF prior to concentrat-

(15) As precedented by the instability of the dimesylate salt.
(16) Concern about the presence of residual borane in the solids, possibly rendering them pyrrophoric, led to this decision.
(17) Due to the solubility of 9-BBN.
(18) Boiling Liquid Escaping Vapor Explosion.
(19) Reisch, M. *Chem. Eng. News* **2002**, *80*, 7.
(20) Sergeyev, S.; Hesse, M. *Synth. Lett.* **2002**, *8*, 1313.

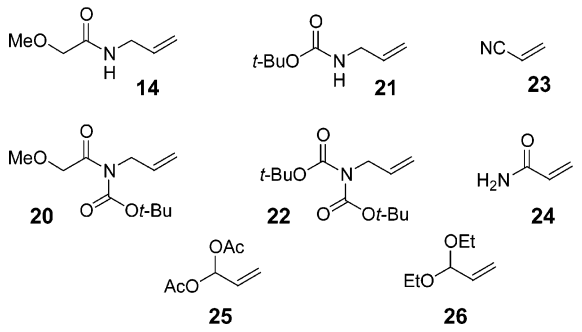


Figure 2. **Olefins screened in the Heck coupling with CP-836,516.**

ing to an oil and chromatographic purification. An estimated 56% in situ yield was achieved. The material was purified by chromatography on silica gel using an ethyl acetate/acetone solvent system to purify the product. Following an acetone crystallization, the sesquisuccinate complex was produced in an acetone/water solvent system. The complex formation proved difficult, and the desired complex only crystallized after three attempts. To achieve a solution that could be filtered through a 1 μm filter prior to crystallization,[21] the solution of CP-724,714 and succinic acid had to be made up more dilute than optimal for crystallization. Following the filtration, the solution was reduced in volume, and a specific final volume and solvent ratio had to be achieved for sesquisuccinate complex to crystallize in preference to the free base (which is also quite insoluble under the crystallization conditions). Separate dissolution followed by filtration of the two components needed for the complex formation was considered as an alternative to the filtration of the mixture, but the two as a mixture proved to be more soluble than the two individually.

Second-Generation Heck Coupling Route. Other olefins which would be expected to couple more cleanly in the Heck reaction were investigated. The low selectivity in the Heck reaction with allylamine methoxyacetamide was not particularly surprising given the literature precedents.[22] We thus turned to an evaluation of several other allylamines (Figure 2).

BOC-protected allylamine **21**[23] reacted with similar selectivity to **14** in the Heck coupling. Acrylamide (**24**) and acrylonitrile (**23**) both coupled cleanly and quickly to provide single products. Acrolein acetals **25** and **26** provided potentially useful results. The bisacetoxy acetal of acrolein **25** coupled to provide two products cleanly: one was the coupled acetal and the other was the coupled aldehyde resulting from acetal deprotection. Finally, bis-BOC allylimide **22** and BOC-allyl methoxyacetamide **20** both coupled cleanly with quinazoline **13** to provide product in >90% in situ yield.

With a number of efficient Heck couplings identified, the products were prioritized for follow up. Three classes of couplings were identified: (1) coupling with an acrolein acetal, the product of which would require deprotection, reductive amination, and amide formation to provide **1**; (2) coupling with acrylamide or acrylonitrile, the products of which would require selective 1,2-reduction with a strong reducing agent followed by amide formation to provide **1**; and (3) coupling with allylamine imides, the products of which would require deprotection (followed by amide formation in the case of **22**) to provide **1**.

Given the mild reaction sequence required to convert the coupling products to the API, the allylamine imide couplings were investigated first. The identity of the amine protecting group influenced the regioselectivity in the Heck coupling. Thus, selectivity of 85:15 was observed in the case of the pthalimide protected allylamine (**28**), 90:10 in the case of BOC-allyl methoxyacetamide (**20**), and 94:6 in the case of bis-BOC allylimide (**22**). The postulate that the selectivity is steric and not electronic in nature was bolstered in the coupling reaction of **29**, which is isosteric with **20** and also gave a 90:10 ratio of products. On the basis of these results, the Heck couplings with **20** and **22** were deemed preferable to phthalimide **28**. Both products were carried forward to **1**, and the bis-BOC allylimide coupling product distinguished itself as a superior synthetic intermediate in a number of ways (see Table 1). Advantages included easier preparation of the starting material (**22**), higher olefin selectivity in the Heck coupling, the opportunity to isolate primary amine **27** with purity upgrade, and the purification of **27** obviating the need for recrystallizations of **1**.

Following Heck coupling of **22** and **13**, the reaction mixture could be extracted with water to remove DMF, then BOC deprotection could be effected in THF with concentrated aq. HCl to afford the HCl salt of primary amine **27** as an off-white, crystalline solid. The overall yield for the Heck coupling, deprotection, and salt formation was 90% on lab scale, with the purity of the solids being >98% by HPLC analysis. As the lab results were quite good, the synthesis was optimized further prior to its implementation on large scale.

Olefin Preparation. The synthesis of the starting bis-BOC allylamine[24] is straightforward; di-*tert*-butyliminodicarboxylate can be treated with KOH to precipitate the potassium salt out of ethanol[25] followed by addition of allylbromide in DMF to afford the desired product.[26] After aqueous work-up, the product can be precipitated from a small volume of cold hexanes as a low-melting solid. This sequence was modified to a one-pot biphasic reaction using aqueous KOH, di-*tert*-butyliminodicarboxylate, MTHF, and allylbromide.[27] The reaction is greatly accelerated by the addition of small amounts of phase-transfer catalyst such as tetrabutylammonium bromide (TBABr, 1.5%) and proceeds to completion in less than 2 h when run at 45 °C. Carrying the reaction mixture into the Heck coupling after solvent

(21) All materials going into the final drug substance crystallization are filtered in solution or neat through a 1 μm filter prior to crystallization per an internal operating procedure.
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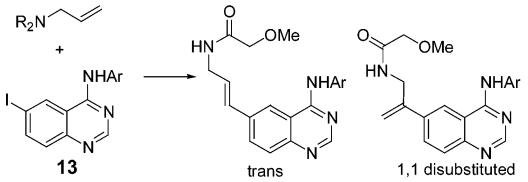
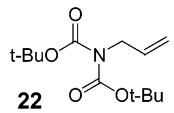
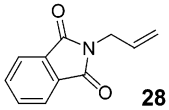
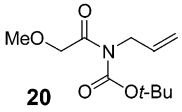
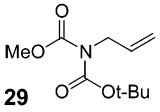
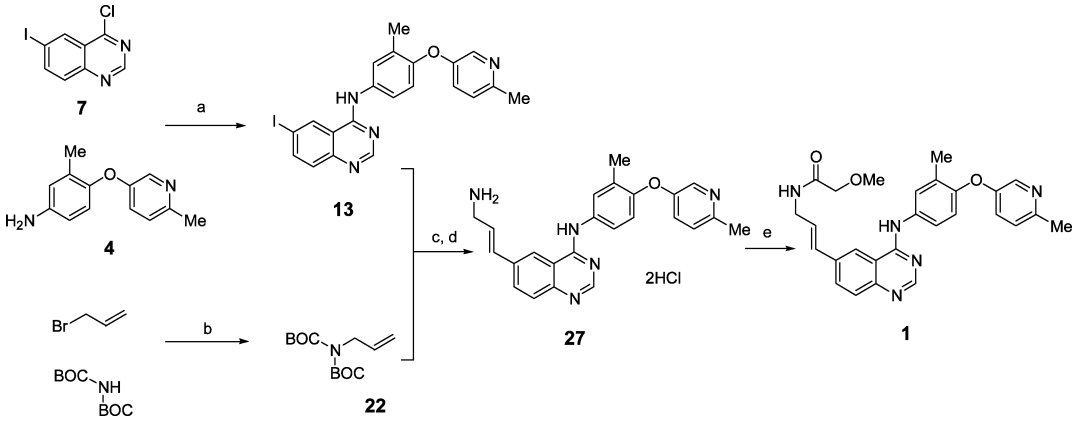
Table 1. **Selectivity of a variety of allylimides in the Heck coupling with quinazoline 13**



Olefin	Ratio (desired : 1,1-disubstituted)	Olefin	Ratio (desired : 1,1-disubstituted)
 **22**	96:4	 **28**	85:15
 **20**	90:10	 **29**	90:10

Scheme 6. **Second-generation Heck coupling route to CP-724,714**[a]



[a] Reagents and conditions: a) IPA, °C, 91−97%; b) MTHF, H_2O, NaOH, Bu_4NCl; c) $Pd_2(dba)_3$, Et_3N, IPA; d) concentrated HCl, 79−84%, two steps; e) MTHF, H_2O, NaOH, $MeOCH_2COCl$, 80%.

exchange is preferred to isolating solids on scale;[28] the crude material which contains 1.5% of a mixture of TBABr and TBAOH actually reacts more rapidly in the Heck coupling than isolated solids which lack the salts.[29]

Heck Coupling/Deprotection. The Heck coupling between **22** and **13** was extensively optimized prior to its execution on scale.[30] The catalyst was switched to $Pd_2(dba)_3$ without added ligand. DMF could be replaced by a number of alcohols including 2-propanol, ethanol, *n*-butanol, *sec*-butanol, and *n*-propanol, as well as acetonitrile and methyl ethyl ketone. Residual MTHF from the previous step (10−20%) was found to retard the rate of reaction, but did not otherwise adversely affect the reaction profile. The alcohols were selected for further study, as residual acetonitrile or ketone solvent from the Heck could result in side reactions during the subsequent deprotection reaction to the primary amine. Triethylamine proved to be the optimal base for the reaction and while the reaction would proceed with 3 equiv of Et_3N, the rate was significantly increased if 5 equiv or more were used. Decreasing the amount of bisBOC allylimide (**22**) to 1.1 from 2 equiv did not significantly decrease the rate of reaction. The Pd loading could be lowered from an initial 5 mol % to less than 1 mol % with a 9 h reaction time. At the end of the reaction, activated carbon (Darco KBB) was added, and the precipitated catalyst was filtered over Celite. The filtrate was diluted with 2-propanol (7 L/kg of **13**), and the BOC groups were removed with aqueous

(28) The solids melt into a solid wax if they are not entirely dried of residual solvent at a low temperature.

(29) This rate acceleration was also observed on the salt-free isolated solids when TBABr was added. The TBABr is likely accelerating the Heck reaction via the Jeffery affect. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(30) A majority of the optimization for the Heck reaction described in this section was conducted on an Anachem SK233 Workstation (www.reactarray.com). In this workstation, up to 10 reactions can be run at once with individual stirring and temperature control. Samples are taken via the liquid handler from the reactions at defined intervals and are quenched and diluted. Online HPLC analyses are then conducted to monitor quantities of starting materials, products, and byproducts. For another study using the Anachem SK233 Workstation, see: Armitage, M. A.; Smith, G. E.; Veal, K. T. *Org. Process Res. Dev.* **1999**, *3*, 189.

HCl (10 equiv). 2-Propanol proved to be superior to THF for the deprotection in three regards: a solvent exchange was unnecessary, tars are not deposited on the reactor, and the deprotection is significantly slower. The slower reaction was advantageous as it maximized the efficiency of the isobutylene scrubber (MsOH/toluene). The acidic conditions in protic solvent, which had previously been demonstrated to decompose **1**, appeared to have the same deleterious effect on any product that did not immediately precipitate. The isolated solids contained 450−550 ppm residual palladium after this procedure. The solids generally had a potency of 85−90%; the remainder of the material was water and some HCl in excess of the 2 equiv tied up as the salt.

As the reaction times and workups for the alkylation, Heck coupling, and deprotection were similar, it was possible to run all three steps in our pilot plant sequentially in one week. Three batches of the alkylation reaction starting with 50 kg of di-*tert*-butyliminodicarboxylate were each carried through the Heck coupling and deprotection to produce **27** as the bis-HCl salt (87.7−91.6 kg, potency 87%) in 79−84% yield (corrected for potency) over the three steps. This sequence will lend itself to semi-batch production on a commercial scale.

Further improvement was made to this reaction after its execution in the pilot plant. The reaction time could be decreased to 3 h with 2.5 equiv of triethylamine if the higher-boiling *n*-propanol (97 °C) or *sec*-butanol (98 °C) were used as solvent; by using *sec*-butanol the deprotection can also be telescoped without solvent replacement as in IPA. The reaction is unaffected by up to 40% water; higher levels result in partial loss of the BOC groups during the Heck coupling and a decrease in reaction rate as solubility becomes an issue. Several types of Pd/C can be used in place of $Pd_2(dba)_3$ with a Pd loading as low as 0.25%. As the reaction can tolerate water, the less hazardous 50% wet catalysts can be used. Even when utilizing the Pd/C catalysts, the residual palladium levels in the isolated product were just as high as the results with $Pd_2(dba)_3$ when run in 2-propanol, but significantly lower when the sequence was run in *sec*-butanol (10 ppm).

Amide Formation. The amide formation was run under Schotten−Baumann conditions with slow addition of the methoxyacetyl chloride to control the heat generated in the reaction. MTHF was used to replace methylene chloride as the reaction solvent. As wet MTHF was also demonstrated to be a very good solvent for the crystallization of **1** with impurity purge, the organic layer could be separated, distilled to a low volume (6 L/kg of **1**), adjusted to a water level of ∼1% v/v by addition of water (measured by KF titration), and the product was precipitated in >99.5% purity with no single impurity greater than 0.3%. The product was filtered in a stirred filter-drier with a containment system to minimize worker exposure to the sensitizing API. Prior to concentration and crystallization, the organic layer of the reaction mixture was treated with 50% w/w activated carbon (Darco KBB) at 65 °C for 18 h to lower the level of residual palladium in the product. The prolonged hot treatment with a high loading of carbon was necessary to lower the palladium levels from the 450−550 ppm level to an acceptable level of 5−10 ppm in the isolated product.

A few new impurities were generated in the amidation step resulting from MOMCl present in the methoxyacetyl chloride.[31] To avoid formation of these impurities and circumvent any residual MOMCl testing which might be required, the acylimidazole of methoxyacetic acid or the anhydride could be utilized to form the desired amide.

Salt Formation. A modified procedure was used to form the salt in the final campaign. Formation of the proper form is sensitive to total reaction volume, water level, and temperature. The salt formation in previous campaigns had presented difficulty when the large volume of water/acetone required for the spec-free filtrations was reduced to the volume needed for the proper form to precipitate. Achieving the tight range for water content and total volume was difficult in those attempts. This problem was circumvented by dissolving the free-base and acid in a lower than required volume of acetone, with enough water for the final crystallization conditions. The drug substance and acid dissolved at a relatively low temperature (∼35 °C) in this solvent system containing a higher water/acetone ratio than required for the crystallization. Acetone could then be added to the solution following filtration to achieve the desired volume and water/acetone ratio for crystallization. This procedure allowed more precise makeup of the crystallization solution, thus leading to good reproducibility on scale. Additionally, as large particles were desired for formulation (100−200 μm needles instead of 10−15 μm needles), an Ostwald ripening[32] procedure was applied to grow the crystal size. After five heating/cooling cycles, the desired particle size was achieved in good uniformity and yield. The larger particles greatly reduced the volume of the isolated solids as well as eliminating problems with fine particles breaking through during filtration.

Conclusion

In comparing the various Pd coupling reactions run, a number of points can be made. Although the Sonogashira coupling was the most facile palladium coupling investigated, the thermal hazards associated with handling acetylenes in conjunction with the need to reduce the acetylene to the *trans*-olefin stood as significant flaws with this approach. The Suzuki coupling route suffered from the same flaws: acetylene intermediates and acetylene reduction were required for this route to be implemented. The olefin geometry was established in high selectivity prior to the coupling reaction. The production of alkylborane byproducts requiring purging (possibly after an oxidative treatment) was a further detriment to this approach. The first-generation Heck chemistry did not suffer from any of these liabilities; however, the poor olefin selectivity in the coupling reaction and difficulty in purification of the product were significant obstacles. In addition, the Suzuki and first-generation Heck

(31) MOMCl is the product of methoxyacetyl chloride decomposition. Stadlwieser, J. *Synthesis* **1985**, *5*, 490. In addition to the hazards associated with MOMCl present in the reagent, one drum of methoxyacetyl chloride actually swelled on storage, presumably due to CO buildup during decomposition.

(32) Ostwald, W. *Lehrbuch Algemeinen Chem.* **1896**, *2*, 444.

Table 2. **Comparison of some key metrics between the four syntheses executed on large scale**

	Sonogashira	Suzuki	1st Heck	bis-BOC Heck
overall yield	11%	17%	12%	~57%
reducing agent required	Red-Al	9-BBN (from borane)	none	none
safety	acetylene reqd. reducing agent	acetylene reqd. reducing agent	no significant hazard	no significant hazard
total waste/kg	1023 L/kg	1105 L/kg	7730 L/kg	132 L/kg
organic waste/kg	900 L/kg	801 L/kg	7716 L/kg	111 L/kg
chlorinated waste/kg	92 L/kg	46 L/kg	0 L/kg	0 L/kg
metal waste produced	Pd, Cu 236 g/kg, 1 equiv Al	Pd 31 g/kg, 1 equiv B	Pd 155 g/kg	Pd 26 g/kg

approaches required that any purification had to be done on the API itself, which had been shown to be a sensitizer. Although less attractive on paper due to the requirement for protecting groups and additional chemistry after coupling, the second-generation route proved to meet all of our process requirements for safety, selectivity, yield, purity, and environmental impact. A summary of these advantages is depicted in Table 2.

As a result of process changes and improvements, 100 kg of CP-724,714 was produced in our pilot facility with high throughput. The final process proceeded in 57% overall yield with a waste production of 132 L/kg of CP-724,714 produced (as compared to ~1100 L/kg for the Sonogashira and Suzuki routes). The process identified has a high margin of safety in its execution from a thermal as well as worker-exposure perspective. Additionally, the amounts of key raw materials required to produce 1 kg of CP-724,714 was reduced by 71%. In general, the utilization of a Heck coupling in place of a Sonogashira or Suzuki coupling for the installation of a trans-disubstituted olefin results in a safer process that produces significantly less metal waste if it can be applied.

Experimental Section

General. Reaction completion and product purity were evaluated by HPLC using the following RP-HPLC conditions: Symmetry Shield RP18, 75 mm × 4.6 mm; flow 1.0 mL/min; 205/210/220/245 nm; temp 25 °C; injection volume: 10 μL of a ca. 0.5% solution in ACN/H_2O 9/1; eluent: B = ACN, C = 0.01 mmol NH_4OAc in H_2O, pH = 6.0; and gradient: 0 min: B = 30%, C = 70%; and 20 min: B = 85%, C = 15%. Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ unless otherwise indicated. IR spectra were recorded as thin films on NaCl plates unless otherwise indicated.

6-(*N*-Methoxyacetyl-3-amino-propen-1-yl)-4-[3-methyl-4-(6-methylpyridine-3-yloxy)phenylamino]quinazoline (1). Amidation method: To [6-(3-Aminopropenyl)quinazolin-4-yl]-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine dihydrochloride (**27**) (6.55 kg, 13.9 mol) was charged 105 L of 2-methyltetrahydrofuran (MTHF), 52 L of water, and NaOH (16.8 kg), and the contents were agitated for 1 h. To the reaction was added methoxyacetyl chloride (2.27 kg, 20.9 mol) while keeping the temperature below 25 °C. The reaction was stirred for 1 h and then assayed by HPLC to confirm reaction completion. The aqueous layer was removed, 3 kg of activated carbon (Darco KBB) was added, and the pot was heated to 72 °C for 18 h. The slurry was cooled to 40 °C, filtered over Celite, and the cake was washed with 20 L of MTHF. The reaction was concentrated atmospherically to 10−15 L final volume, cooled to 10 °C over 4 h, granulated for 8 h, and then filtered on a stirred filter/drier. The cake was washed with 13 L of MTHF and then dried at 45 °C with a nitrogen sweep under vacuum. The product was isolated in 80% (5.24 kg, 11.1 mol). R_f = 0.16 (silica gel, EtOAc/MeOH = 9/1). ^{1}H NMR ($CDCl_3$, 250 MHz) δ = 8.71 (s, 1H), 8.25 (d, J = 1.7 Hz, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.79 (s, 1H), 7.66 (d, J = 2.5 Hz, 1H), 7.54 (dd, J = 8.7, 2.6 Hz, 1H), 7.15−7.07 (m, 2H), 6.91 (d, J = 8.7 Hz, 1H), 6.83 (bt, 1H), 6.65 (d, J = 15.9 Hz, 1H), 6.34 (dt, J_d = 15.9 Hz, J_t = 6.1 Hz, 1H), 6.29 (dt, J_d = 15.9 Hz, J_t = 6.1 Hz, 1H), 4.14 (dt, J = 6.1 Hz, 2H), 3.97 (s, 2H), 3.45 (s, 3H), 2.53 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 169.76, 157.90, 154.93, 152.367, 152.23, 150.90, 149.74, 139.34, 134.73, 134.63, 131.16, 130.77, 130.36, 128.85, 129.98, 125.47, 124.66, 123.65, 121.32, 119.51, 119.13, 115.39, 71.96, 59.26, 40.84, 23.57, 16.41. IR (powder) 3350, 3138 (br), 2997, 2926, 2824, 1640, 1574, 1531, 1476, 1423, 1386, 1270, 1209, 1196, 1122, 1070, 961, 938, 883, 826, 802 cm^{-1}. Anal. calcd (found): C, 69.07 (68.96); H, 5.80 (5.76); N, 14.92 (14.89). HPLC t_R (min) 6.02; mp 75−95 °C.

Suzuki Coupling Method. To a dry and oxygen-free reaction vessel was added 6-iodo-quinazolin-4-yl)-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine hydrochloride (**13**) (10.3 g, 20.4 mmol) in tetrahydrofuran (40 mL). In another reaction vessel *N*-propargyl-2-methoxyacetamide (**16**) (5.0 g, 39.3 mmol) was added to a 1.0 M solution of 9-BBN (86.5 mL, 86.5 mmol) and warmed to 30 °C for 2 h. A solution of potassium carbonate (28.4 g, 205.6 mmol) in water (40 mL) was prepared. The solution of potassium carbonate was added to the 9-BBN/*N*-propargyl-2-methoxyacetamide solution. The potassium carbonate/*N*-propargyl-2-methoxyacetamide solution was added to the THF/6-iodo-quinazolin-4-yl)-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine hydrochloride (**13**) slurry. A solution of $Pd_2(dba)_3$ (1.8 g, 1.96 mmol) in THF (40 mL) was added to the reaction. The contents were heated to 50−55 °C. The reaction was complete in 5−6 h by HPLC.

The bottom aqueous layer was removed, and the organic layer was washed with a pH 2−4 acidic aqueous solution.

The organic layer was washed with 50 mL of CH_2Cl_2, and the organic layer was removed. The aqueous layer was basified to pH 10−12 with sodium hydroxide, and the water layer was extracted two times with 100 mL of CH_2Cl_2 and concentrated to an oil (8.55 g, 85% potency, 55% yield based on potency).

Heck Coupling Method. To a 200-L reaction vessel was charged (6-iodo-quinazolin-4-yl)-[3-methyl-4-(6-methyl-pyridin-3-yloxy)phenyl]amine hydrochloride (**13**) (15.0 kg, 32.0 mol), *N*-allyl-2-methoxyacetamide (**14**) (4.94 kg, 38.2 mol), sodium acetate (7.88 kg, 96.1 mol), $Pd_2(dba)_3$ (1.17 kg, 1.28 mol), triethylamine (54.0 kg, 528 mol), and 2-B ethanol[33] (90 L). The mixture was heated to 70 °C, held for 6 h, cooled to 40 °C, and filtered through Celite. Two batches were combined, and the liquors were concentrated and chromatographed on silica gel using an ethyl acetate/acetone solvent system. Following chromatography, the product-rich fractions were concentrated, and the desired product was crystallized from acetone. The final product was isolated in 36% yield (10.4 kg, 23.3 mol).

6-(*N*-Methoxyacetyl-3-aminopropen-1-yl)-4-[3-methyl-4-(6-methylpyridine-3-yloxy)phenylamino]quinazoline Sesquisuccinate (1·1.5 Succinate). 6-(*N*-Methoxyacetyl-3-aminopropen-1-yl)-4-[3-methyl-4-(6-methyl-pyridine-3-yloxy)phenylamino]quinazoline sesquisuccinate (**1**) (24.0 kg, 51.1 mol) and succinic acid (18.1 kg, 153 mol) were dissolved in 8.9 gal of water and 82 gal of acetone at 45 °C. The solution was filtered through a 1 μm filter, and an additional 13 gal of acetone was added. With slow stirring, the solution was cooled to 43 °C and 240 g (1 wt %) of 6-(*N*-methoxyacetyl-3-aminopropen-1-yl)-4-[3-methyl-4-(6-methylpyridine-3-yloxy)phenylamino]quinazoline sesquisuccinate (1·1.5 succinate) was added. The slurry was held at 43 °C for 2 h and then cooled to 20 °C over 1 h. The slurry was reheated to 38 °C over 1 h, held for 1 h, and then cooled to 20 °C over 1 h and held for 45 min. This heating/cooling cycle was repeated twice more, and then the pot was heated to 38 °C and cooled to 33 °C over 3 h, 29 °C over 2 h, 24 °C over 1 h, and to 0 °C over 4 h. The slurry was stirred for 3 h, filtered on a filter dryer, and rinsed with 13 gal of acetone. After drying for 18 h at 45 °C, 28.2 kg of product (43.4 mol) was isolated in 85% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ = 8.39 (s, 1H), 8.13 (s, 1H), 8.07−8.08 (m, 1H), 8.16 (s, 1H), 7.77 (dd, J = 1.6, 8.7 Hz, 1H), 7.53−7.60 (m, 3H), 7.18−7.22 (m, 2H), 6.87 (d, J = 8.3 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 6.40 (dt, J_d = 16.0 Hz, J_t = 5.6 Hz, 1H), 5.24 (br, s, 4H), 4.04 (d, J = 5.0 Hz, 2H), 3.95 (s, 2H), 2.55 (s, 6H), 2.45 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ = 174.43, 169.72, 158.23, 154.77, 152.74, 152.39, 150.28, 149.44, 138.99, 136.10, 135.36, 131.48, 129.87, 129.75, 129.30, 128.38, 126.06, 125.07, 124.45, 122.32, 120.69, 119.98, 115.82, 72.24, 59.29, 40.72, 29.46, 23.56, 16.60. IR (powder) 3294, 2927, 2465 (br) 1931 (br), 1698, 1637, 1572, 1532, 1491, 1423, 1385, 1358, 1262, 1217, 1171, 1119, 957, 836, 826, 802, 670 cm^{-1}. Anal. calcd (found): C, 61.29 (61.28); H, 5.61 (5.43); N, 10.83 (10.77). HPLC t_R (min) 6.02; mp 143 °C.

(33) Toluene denatured ethanol.

3-(2-Methyl-4-aminophenoxy)-6-methylpyridine (4): ^{1}H NMR (CD_3OD, 400 MHz) δ =7.96 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.11 (dd, J = 8.3, 2.9 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.66 (d, 1H, J = 2.9 Hz), 6.58 (dd, J = 8.3, 2.5 Hz, 1H), 4.90 (s, 2H), 2.44 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz) δ = 154.16, 150.84, 145.32, 144.84, 137.02, 130.80, 124.19, 124.00, 121.50, 117.98, 114.11, 22.03, 15.48. IR (powder) 3422 (br), 3328 (br), 3199 (br), 1640, 1610, 1571, 1500, 1480, 1386, 1254, 1235, 1217, 1201, 1160, 1130, 1024, 863, 820, 802, 721 cm^{-1}. Anal. calcd (found) C, 72.87 (72.79); H, 6.59 (6.42); N, 13.07 (12.98); mp 95−97 °C.

(3-{4-[3-Methyl-4-(6-methylpyridin-3-yloxy)phenylamino]quinazolin-6-yl}prop-2-ynyl)carbamic Acid *tert*-Butyl Ester (10). To a clean and dry nitrogen-purged 300-gal glass-lined reactor was charged 5.7 kg (20 mol) of 4-chloro-6-iodoquinazoline (**7**), 247 g (0.35 mol) of *trans*-bis-triphenylpalladium chloride, and 67 g (0.35 mol) of CuI. To this was charged 25 gal of THF and a slurry of *N*-propargyl-2-methoxyacetamide (16) in 12 L of THF (5.0 kg, 32 mol). To the slurry was charged 3.3 L (2.4 kg, 23 mol) of diisopropylamine chased with 2 gal of THF. The reaction mixture was stirred at 22−23 °C for 3 h. The reaction was sampled for HPLC and then filtered via an 18-in. diameter sparkler filter precoated with Celite to a clean and dry nitrogen-purged 100-gal reactor. The filter and lines were rinsed with 10 gal of THF and then concentrated atmospherically to 15 gal. To the crude oil was charged 30 gal of toluene and 6.0 kg of Darco KBB. The slurry was heated to 85 °C and held for 1 h. The batch was cooled to 60 °C and then filtered via an 18 in. diameter sparkler precoated with 60 °C toluene and Celite. The filtrate was concentrated to 5 gal and held for the next step. Some product was caught in the carbon cake so the Darco cake was reslurried in hot ethyl acetate and refiltered. The product-rich ethyl acetate solution was combined with the toluene solution and carried on to the next step.

To a nitrogen-purged and clean 100-L glass-lined reactor was charged the product-rich ethyl acetate and toluene solution from the previous step. The solution was concentrated via full vacuum and concentrated to 4−10 L of oil. To the reaction mixture was charged 41 L of *tert*-butyl alcohol and 41 L of dichloroethane. To this solution was charged 2.1 kg (9.8 mol) of 3-(2-methyl-4-aminophenoxy)-6-methylpyridine (**4**), and the solution was stirred at 26 °C for 1.5 h. The reaction was judged incomplete (all the 3-(2-methyl-4-aminophenoxy)-6-methylpyridine (**4**) was consumed) by HPLC so another 100 g (0.47 mol) of 3-(2-methyl-4-aminophenoxy)-6-methylpyridine (**4**) was added to the reaction. The reaction mixture was stirred another 1.5 h. The reaction mixture was then concentrated to 8 L under vacuum. The crude product was diluted with 50 L of ethyl acetate, heated to reflux for 1 h, and then allowed to stir at 0 °C overnight. The product was isolated (3.56 kg, 14.6 mol, 73%) via filtration and washed with 4 L of EtOAc. Palladium and copper levels were both under 50 ppm as measured by ICPMS analysis. ^{1}H NMR (d_6-DMSO, 400 MHz) δ = 9.87 (s, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 8.16 (s, 1H), 7.80−7.77

(m, 2H), 7.73−7.68 (m, 2H), 7.45 (br t, J = 5.8 Hz, 1H), 7.24−7.17 (m, 2H), 6.94 (d, J = 8.7 Hz, 1H), 4.05 (d, J = 5.8 Hz, 2H), 2.42 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ = 157.78, 156.02, 155.86, 152.73, 152.48, 150.34, 149.89, 139.18, 136.05, 135.84, 129.68, 128.89, 126.97, 125.94, 125.03, 124.45, 122.19, 120.64, 119.98, 115.75, 89.49, 81.70, 79.01, 30.82, 28.85, 23.77, 16.72. IR (powder) 3308, 3194, 3006, 1677, 1574, 1530, 1501, 1480, 1420, 1361, 1284, 1251, 1223, 1195, 1167, 1115, 832, 786, 661 cm^{-1}; mp 141 °C dec.

(6-Iodo-quinazolin-4-yl)-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine Hydrochloride (13). In a 300-gal reactor, 4-chloro-6-iodoquinazoline (**7**) (49.9 kg, 172 mol), 3-(2-methyl-4-aminophenoxy)-6-methylpyridine (**4**) (36.8 kg, 172 mol), and ^{i}PrOH (200 gal) were heated to reflux for 2 h and then cooled to 25 °C over a period of 6 h. The slurry was filtered, and the cake was washed with 25 gal of ^{i}PrOH. After drying at 55 C for 24 h, 83.1 kg of desired material (164 mol, 95.8%). R_f = 0.45 (silica gel, EtOAc/MeOH = 9/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 11.40 (br, s, 1H), 9.29 (m, 1H), 8.91 (s, 1H), 8.36−8.32 (m, 2H), 7.74−7.73 (m, 2H), 7.62 (dd, J_1 = 8.7, 2.6 Hz, 1H) 7.49−7.46 (m, 2H), 7.06 (d, J = 8.7 Hz, 1H), 2.54 (s, 3H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$ + d_6-DMSO, 75 MHz) δ = 159.51, 153.63, 153.17, 152.82, 152.70, 145.26, 141.37, 138.01, 134.75, 134.65, 131.05, 129.10, 128.74, 126.77, 124.86, 124.43, 120.41, 116.98, 94.89, 23.54, 17.67. RP-HPLC t_R (min) 12.13. IR (powder) 3098 (br), 1570, 1529, 1476, 1416, 1387, 1376, 1354, 1262, 1226, 1211, 1196, 1134, 1115, 1016, 824, 792, 721, 667 cm^{-1}. Anal. calcd (found): C, 53.86 (53.87); H, 3.66 (3.47); N, 11.96 (11.77); I, 27.10 (27.27); mp 220−253 °C dec.

***N*-Allyl-2-methoxyacetamide (14).** To a solution of allylamine (2.50 kg, 43.8 mol) and triethylamine (4.92 kg, 48.2 mol) in MTHF (32 L) was added methoxyacethyl chloride (5.23 kg, 48.2 kg) at −10 to 25 °C. The reaction was stirred for 4 h, washed with 1 N HCl (6.00 kg) followed by 1 N NaOH (7.55 kg), and MTHF was distilled atmospherically until the water content was <0.5% (KF). The material was carried into the next step in solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.60 (br, s, 1H), 5.84 (ddt, 1H, J_t = 5.2 Hz, J_d = 10.4, 17.6 Hz), 5.20 (dq, J_d = 16.8 Hz, J_q = 1.6 Hz, 1H), 5.14 (dq, J_d = 10.4 Hz, J_q = 1.6 Hz, 1H), 3.94−3.91 (m, 1H), 3.91 (s, 3H), 3.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 169.46, 134.14, 116.35, 72.03, 59.26, 41.17. IR (neat) 3307 (br), 3080, 2987, 2916, 2826, 1660, 1524, 1451, 1428, 1278, 1198, 1112, 989, 922 cm^{-1}. Anal. calcd (found): C, 55.80 (55.50); H, 8.58 (8.87); N, 10.84 (10.85).

***N*-Propargyl-2-methoxyacetamide (16).** To a 250-mL reactor was added 2-methyl-THF (90 mL), propargylamine (1.6 g, 27.9 mmol), and triethylamine (3.10 g, 30.7 mol). The reaction vessel was cooled to −15 to −5 °C, and a solution of methoxyacetyl chloride (3.33 g, 30.7 mol) in MTHF (10 mL) was added via an addition funnel *slowly* while keeping the temperature in the reaction below −5 °C. The reaction was heated to 20−25 °C, stirred for 4 h, washed with 1 N HCl (10 mL) followed by 1 N NaOH (10 mL), and MTHF was distilled atmospherically until the water content was <0.5% (KF). The material was carried into the next step in solution. R_f = 0.36 (silica gel, heptane/EtOAc = 7/3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.72 (br, s, 1H), 4.09 (dd, J = 5.5, 2.6 Hz, 2H), 3.92 (s, 2H), 3.43 (s, 3H), 2.24 (t, J = 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 169.14, 79.11, 71.63, 71.41, 59.04, 28.26. IR (neat) 3286 (br), 2936, 2829, 1665, 1526, 1199, 1115 cm^{-1}.

Allylmethoxyacetylcarbamic Acid *tert*-Butyl Ester (20). *N*-Allyl-2-methoxyacetamide (**14**) (6.95 g, 54 mmol) was dissolved in a solution of dry CH_2Cl_2 (100 mL). 4-(Dimethylamine)pyridine (54 mmol, 6.6 g) and Et_3N (5.5 g, 54 mmol) were added to the solution. The solution was cooled to 0 °C, and BOC_2O (108 mmol, 23.6 g) was added dropwise. The solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was diluted with 100 mL of H_2O and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solvents were removed in vacuo to give an oil. This material was then chromatographed on silica gel, eluting with 10−20% EtOAc/hexane to give 6.6 g of (54%) of title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.60−5.65 (m, 1H), 4.96−5.02 (m, 2H), 4.38 (s, 2H), 4.15 (d, J = 4.5 Hz, 2H), 3.30 (s, 3H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 172.74, 152.78, 133.07, 117.08, 83.66, 74.35, 59.30, 46.26, 28.06. IR (neat) 2980, 1728, 1720, 1368, 1338, 1222, 1199, 1144, 1100, 991, 938, 852, 779 cm^{-1}. Anal. calcd (found): C, 57.62 (57.36); H, 8.35 (8.45); N, 6.11 (6.03).

***N*,*N*-Bis(*tert*-butoxycarbonyl)allylamine (22).** To a 200-gal reactor were charged di-*tert*-butyliminodicarboxylate (50.0 kg, 230 mol), allyl bromide (33.4 kg, 276 mol), terabutylammonium bromide (1.11 kg, 3.45 mol), NaOH (50% w/w, 24.3 gal, 1150 mol), water (66 gal), and MTHF (66 gal), and the mixture was heated to 42 °C for 2 h with rapid agitation. The aqueous layer was removed, and the material was concentrated atmospherically to a volume of 50 gal. The solution was filterd through a 1 μm filter, and 24 gal of ^{i}PrOH was added. The solution was concentrated to a final volume of ∼20 gal, and an additional 53 gal of ^{i}PrOH was added. This solution was used as is in the next step of the process. The yield was 95−98%. Spectral data was comparable to that reported in the literature.

[6-(3-Aminopropenyl)quinazolin-4-yl]-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine Dihydrochloride (27). To a 300-gal reactor was charged (6-iodo-quinazolin-4-yl]-[3-methyl-4-(6-methylpyridin-3-yloxy)phenyl]amine hydrochloride (**13**) (101.0 kg, 200.0 mol), *N*,*N*-Bis(*tert*-butoxycarbonyl)allylamine (22) (solution as prepared above, ∼220 mol), $Pd_2(dba)_3$ (1.83 kg, 2.00 mol), triethylamine (102.0 kg, 1000 mol), and ^{i}PrOH (160 gal), and the headspace was well purged with nitrogen. The reaction was heated to 78 °C for 18 h. The mixture was cooled, activated carbon (Darco KBB, 15.0 kg) was charged, and the mixture has heated to 50 °C for 3 h. The mixture was filtered through Celite and diluted with 135 gal of ^{i}PrOH. Concentrated HCl (54.3 gal, 2500 mol) was added and the reaction was heated to 40 °C for 14 h. The off-gasses were swept with nitrogen through a toluene/methanesulfonic acid scrubber. The reaction was cooled to 20 °C and filtered, and the cake was washed with

27 gal of ^{i}PrOH. After drying at 40 °C for ~60 h, the product was isolated (91.6 kg, 194 mol, 97% yield uncorrected for potency). ^{1}H NMR (300 MHz, D_2O) δ = 8.53 (s, 1H), 8.35 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 9 Hz, 1.5 Hz, 1H), 7.99 (dd, J = 9 Hz, 2.7 Hz, 1H), 7.69−7.74 (m, 2H), 7.48 (d, J = 2.7 Hz, 1H), 7.38 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 7.16(d, J = 8.7 Hz, 1H), 6.9 (d, J = 16.2 Hz, 1H), 6.5 (dt, J = 16.2 Hz, 6.6 Hz, 1H), 2.61 (s, 3H), 2.14 (s, 3H). IR (powder) 3438 (br), 2800 (br), 2623, 1616, 1569, 1553, 1527, 1493, 1436, 1377, 1354, 1313, 1267, 1245, 1193, 1114, 976, 869, 840, 806, 782, 694, 653 cm^{-1}.

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