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Synthesis of 7-(*E*)-alkenyl-4-amino-3-quinolinecarbonitriles via Pd-mediated Heck, Stille, and Suzuki reactions

Yanong D. Wang *, Minu Dutia, M. Brawner Floyd, Amar S. Prashad, Dan Berger, Melissa Lin

Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, NY 10965, United States

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ABSTRACT

A regio- and stereoselective synthesis of 7-(*E*)-alkenyl-4-amino-3-quinolinecarbonitriles via Pd-mediated coupling reactions was developed. The comparison and optimization of stereoselectivity of the Heck, Stille, and Suzuki reactions of 7-bromo or 7-triflate-3-quinolinecarbonitrile are described. Compound **7** and **10** were potent inhibitors of Src kinase and Raf/Mek activity, respectively.

1. Introduction

Protein tyrosine kinases (PTKs) are key enzymes in signal transduction pathways regulating a number of cellular functions such as cell growth and differentiation. Kinase over-expression or mutations are often associated with various diseases. Small molecule inhibitors of protein kinases have shown great therapeutic potential for treatment of diverse disease states, especially cancer.[1–4] Miscellaneous scaffolds have been used as templates for development of kinase inhibitors, for example, 4-anilino-3-quinolinecarbonitrile, a privileged kinase scaffold discovered at Wyeth.[5,6] It was observed that variation of substituents on the 4-anilino group of 3-quinolinecarbonitrile had a major impact on the kinase specificity. SKI-606 (**1**)[7–9] (Fig. 1), currently in clinical trials as an anti-cancer agent, is a potent inhibitor of Src kinase. We have also reported the potent inhibition of Mek kinase by the 7-alkoxy-4-anilino-3-quinolinecarbonitrile (**2**).[10] In order to further probe the SAR of 3-quinolinecarbonitriles as kinase inhibitors, compounds possessing an (*E*)-alkenyl group at the C-7 position of 3-quinolinecarbonitrile scaffold, exemplified by structure **3**, were therefore designed as potential Src or Mek inhibitors.

2. Results and discussion

The Pd-mediated arylations of alkenes, including Heck, Stille, and Suzuki reactions, have received a great deal of attention in the last two decades and have been applied to the synthesis of a wide range of biologically interesting compounds.[11,12] These reactions can be broadly defined as the Pd-catalyzed coupling of organic electrophiles (such as alkenyl or aryl (sp^2) halides or triflates) with alkenes (Heck reaction[13,14]) or alkene equivalents, such as vinylstannane (Stille reaction[15,16]) or vinylboron compounds (Suzuki reaction[17,18]).

We envisioned that 7-(*E*)-alkenyl-3-quinolinecarbonitrile (**3**) could be effectively assembled via the coupling reaction of a 7-bromo (or triflate)-3-quinolinecarbonitrile intermediate (**A**) and an alkenyl building block (**B**, **C** or **D**) (Fig. 1).

2.1. Heck reaction

As depicted in Scheme 1, 1-(but-3-enyl)-4-methylpiperazine (**5**) was prepared by treatment of 4-bromobut-1-ene with *N*-methylpiperazine.[19] Under typical Heck conditions, the coupling reaction of 7-triflate-3-quinolinecarbonitrile (**6**)[20] with **5** gave a mixture of *E*/*Z* isomers of **7** along with a double bond migration by-product (**8**) as an inseparable 70:15:15 (***E*-7**/***Z*-7**/**8**) mixture as determined by LC–NMR. The predominant ***E*-7** product is obtained by an addition–elimination mechanism, in which the β-hydride elimination is stereoselective and occurs in a *syn* manner.[14,21] The formation of double bond isomerization product (***Z*-7**) and double bond migration product (**8**) is likely due to a reversible β-hydride elimination process and a sluggish dissociation step of the olefin from the Pd(II)-H species.[22] Similar results were reported on unsymmetrical non-functionalized alkenes.[23,24] The coupling of **9** and **5** provided a 35% yield of products **10** (***E*+*Z***) and **11** in an analogous ratio of 80:10:10 (***E*-10**/***Z*-10**/**11**).

2.2. Stille reaction

The unsatisfactory product mixtures obtained by the Heck reactions of **6** and **9**[25]prompted us to investigate the alternative Stille coupling reaction. The Pd-mediated Stille reaction has been widely used for the synthesis of complex molecules, due to typically mild reaction conditions, the tolerance of functional groups, and the ease

* Corresponding author. Tel.: +1 845 602 5253; fax: +1 845 602 5561.
E-mail address: wangd@wyeth.com (Y.D. Wang).

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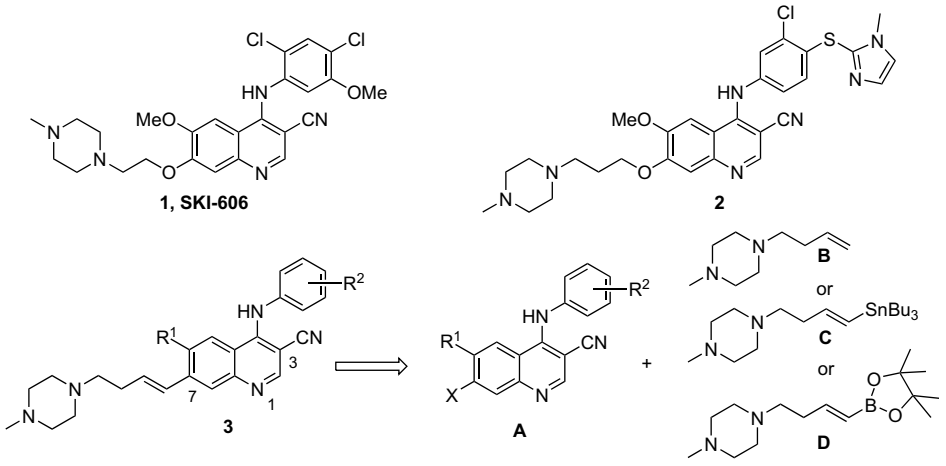
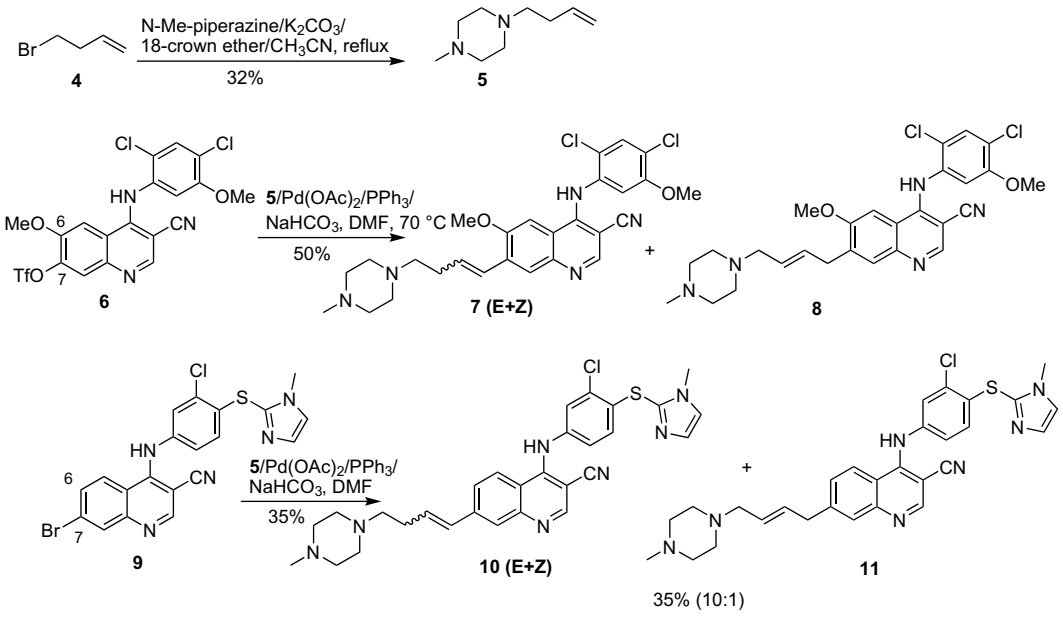


Figure 1.



Scheme 1.

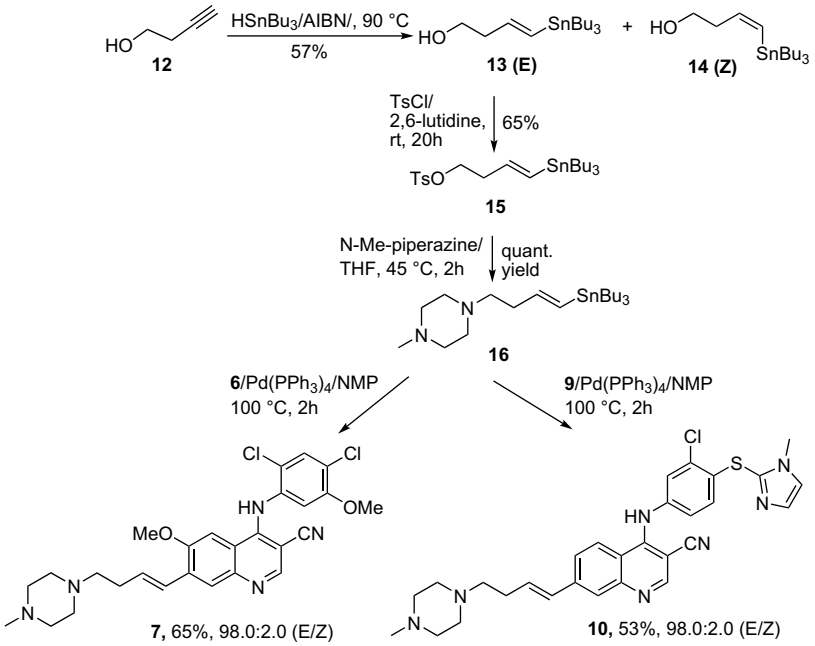
of preparation of vinylstannanes. Hydrostannation of but-3-yn-1-ol readily provided (*E*)-vinylstannane (**13**)[26] as the major product, along with a minor product of (*Z*)-vinylstannane (**14**) (Scheme 2). Separation of the isomers was achieved by column chromatography. Tosylation of **13** followed by amination with *N*-methylpiperazine afforded vinylstannane **16**.

The Stille coupling reaction between **6** and **16** produced 7-(*E*)-alkenyl-3-quinolinecarbonitrile **7** in 65% yield with an *E*/*Z* ratio of 98.0:2.0 as determined by HPLC and ^{1}H NMR. Using the same procedure, reaction of **9** and **16** afforded **10** in 58% yield, with an equal *E*/*Z* ratio of 98.0:2.0. Double bond migration products were not observed in this reaction. It is known in the literature[27] that the Stille coupling reaction is stereospecific, where the *E*/*Z* ratio of product is typically correlated with the *E*/*Z* ratio of vinylstannane. Thus, we postulated that 2% of the *Z*-isomer observed in these coupling reaction was likely due to the contamination by the *Z*-isomer of vinylstannane. Nonetheless, this methodology represented a significant improvement over the Heck reaction as a means of providing our target compounds with excellent stereoselectivity.

2.3. Suzuki reaction

To avoid the necessity of a tedious chromatographic separation of (*E*) and (*Z*)-isomers in the Stille protocol, we embarked on an investigation of the Suzuki reaction. As an effective tool for C–C bond formation, the Suzuki reaction has also been used extensively because vinylboronic esters (acids) can be prepared with high regio- and stereoselectivity under relatively mild reaction conditions. We have previously described[28] an efficient stereoselective synthesis of (*E*)-vinylboronic esters via a Zr-mediated hydroboration of alkynes. Thus, aminoalkyne (**17**)[29] was converted to (*E*)-vinylboronic ester (**19**) (<1% of *Z* isomer as determined by ^{1}H NMR) (Scheme 3), which can be used for the next step without further purification.

Reaction conditions, including solvents, Pd catalysts, reaction temperature, and time, were examined in order to optimize this chemistry. We have found that compounds **7** and **10** can be prepared in a one-pot protocol in which vinylboronic ester **19** was generated in situ. It is noteworthy that a particular solvent system (toluene/ethanol/water, 10:1:1) is crucial in this coupling reaction to accommodate the solubility requirement of all substrates and reagents and to



Scheme 2.

ensure complete conversion. Under the optimal coupling reaction conditions ($Pd(PPh_3)_4/NaHCO_3$/toluene/EtOH/H_2O, 90 °C, 4 h), coupling of **6** and **19** provided the target product (**7**) in 76% yield. Likewise, compound **10** was obtained from **9** and **19** in 63% yield. In both cases, only trace amount of *Z*-isomer (<1%) was observed.

2.4. Biological activity of 7 and 10

In a Lance format Src enzymatic assay,[30] compound **7** had an IC_{50} value of 2.1 nM. It was also found that **7** inhibited cell growth in a Src-dependent cell proliferation assay[30] with an IC_{50} of 58 nM. Compound **10** was a potent inhibitor of Raf/Mek activity, having an IC_{50} of 19 nM in an enzymatic assay[31] and an IC_{50} of 14 nM in a Lovo cellular assay.[31] A full account of their biological activities and SAR will be disclosed in a separate report.

In summary, we present here a synthesis of 7-(*E*)-alkenyl-3-quinolinecarbonitriles using Pd-mediated coupling reactions. We have evaluated the stereoselectivity of Heck, Stille, and Suzuki coupling reactions of two 7-Br (or OTf)-3-quinolinecarbonitriles. Under the optimized reaction conditions, 7-(*E*)-alkenyl-3-quinoline-carbonitriles (**7** and **10**) were prepared efficiently with excellent regio- and stereoselectivity.

3. Experimental

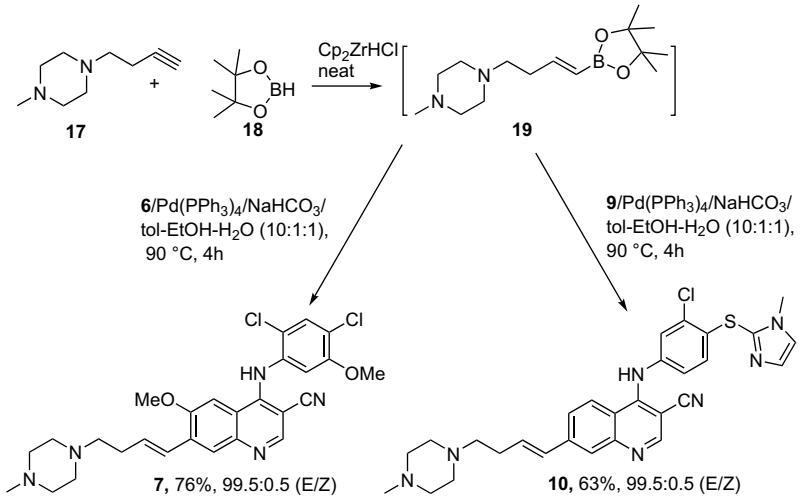
3.1. General

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a NT-300 WB spectrometer. Electrospray (ES) mass spectra were recorded on a Microma Platform mass spectrometer. Flash chromatography was performed with Baker 40 μM silica gel. Reactions were generally carried out under an inert atmosphere of nitrogen.

3.2. Heck reaction: compounds 6, 7, 10

*3.2.1. 1-(But-3-enyl)-4-methylpiperazine (**5**)*

A mixture of *N*-methylpiperazine (2.0 g, 20 mmol), 4-bromobut-1-ene (**4**) (3.24 g, 24 mmol), 18-crown ether (0.26 g, 1 mmol), and



Scheme 3.

potassium carbonate (4.2 g, 30 mmol) in acetonitrile (20 mL) was heated at reflux overnight. The resulting mixture was filtered through a pad of silica gel and the filtrate was concentrated, which turned into a mixture of oil and solid. The mixture was filtered and washed with hexane. The filtrate was concentrated to provide 1.0 g of **5** (32%) as an oil. ^{1}H NMR (δ, DMSO-d_6): 5.79 (m, 1H), 5.04 (dd, J=26, 2.2 Hz, 1H), 4.98 (dd, J=22, 2.1 Hz, 1H), 3.33 (s, 3H), 2.50 (t, J=2.0 Hz, 3H), 2.33 (m, 8H), 2.19 (m, 2H).

3.2.2. Method A: 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-enylquinoline-3-carbonitrile (*E*-7/*Z*-7/*8*)

To a mixture of $NaHCO_3$ (19 mg, 0.23 mmol), PPh_3 (8.0 mg, 0.029 mmol), and $Pd(OAc)_2$ (4.0 mg, 0.019 mmol) were added **5** (36 mg, 0.23 mmol) and **6** (100 mg, 0.19 mmol) in DMF (2.0 mL) via syringe. The reaction mixture was heated at 70 °C for 15 h and partitioned between EtOAc and aqueous NH_4Cl. The combined organics were dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography to give 50 mg yellow solid (50%) of ***E*-7**/***Z*-7**/**8** as an inseparable mixture; mp 208 °C. The mixture of ***E*-7**/***Z*-7**/**8** was analyzed by LC–NMR.

LC–NMR was performed on a Bruker AVANCE 600 MHz spectrometer equipped with a 4 mm i.d. flow probe with an active volume of 120 μl. All LC–NMR experiments were conducted using loop storage mode. Proton NMR spectra were acquired using a 1D NOESYPRESAT sequence to achieve solvent suppression. HPLC analysis was performed on an Agilent Model 1100 HPLC system equipped with an autosampler, binary pump, and a variable wavelength detector monitoring at 254 nm. Chromatographic separation was carried out using a 5 μm 4.6×150 mm XTerra RP_{18} column under isocratic conditions consisting of 87% D_2O and 13% acetonitrile-d_3 with 0.02% TFA buffer.

^{1}H NMR of ***E*-7** (δ, DMSO-d_6): 9.81 (br s, 1H), 8.40 (s, 1H), 7.95–7.66 (m, 3H), 7.33 (br s, 1H), 6.82 (d, J=16 Hz, 1H), 6.59 (m, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.49 (m, 2H), 2.50–2.30 (m, 10H), 2.18 (s, 3H).

^{1}H NMR of ***Z*-7** (δ, DMSO-d_6): 9.81 (s, 1H), 8.41 (s, 1H), 7.88 (s, 1H), 7.85 (s, 1H), 7.75 (s, 1H), 7.35 (s, 1H), 6.61 (d, J=11.8 Hz, 1H), 5.91 (dt, J=11.8, 6.4 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.45 (m, 2H), 2.42 (m, 2H), 2.34 (br, 8H), 2.16 (s, 3H).

^{1}H NMR of **8** (δ, DMSO-d_6): 9.81 (s, 1H), 8.42 (s, 1H), 7.85 (s, 1H), 7.75 (s, 1H), 7.67 (s, 1H), 7.35 (s, 1H), 5.80 (dt, J=15.6, 6.7 Hz, 1H), 5.52 (dt, J=15.6, 6.7 Hz 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.48 (d, J=6.7 Hz, 2H), 2.92 (d, J=6.7 Hz, 2H), 2.34 (br, 8H), 2.16 (s, 3H).

3.2.3. 4-({3-Chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-7-[4-(4-methylpiperazin-1-yl)but-1-enyl]quinoline-3-carbonitrile (*E*-10/*Z*-10/*11*)

Following the procedure used to prepare **7**/**8** (method A), ***E*-10**/***Z*-10**/**11** was obtained from **9** and **5** as a pale yellow solid (35%); mp 218 °C.

^{1}H NMR of ***E*-10** (δ, DMSO-d_6): 9.86 (s, 1H), 8.59 (s, 1H), 8.30 (d, J=8.7 Hz, 1H), 7.80 (s, 1H), 7.79 (d, J=8.7 Hz, 1H), 7.54 (d, J=1.1 Hz, 1H), 7.44 (s, 1H), 7.16 (d, J=1.1 Hz, 1H), 7.15 (m, 1H), 6.64 (m, 2H), 6.54 (d, J=8.6 Hz, 1H), 3.61 (s, 3H), 2.37 (m, 12H), 2.15 (s, 3H). Anal. Calcd for $C_{29}H_{30}ClN_7S$: C, 64.01; H, 5.56; N, 18.02. Found: C, 64.01; H, 5.52; N, 17.68.

^{1}H NMR of ***Z*-10** (δ, DMSO-d_6): 9.90 (s, 1H), 8.62 (s, 1H), 8.37 (d, J=8.6 Hz, 1H), 7.91 (s, 1H), 7.61 (d, J=8.6 Hz, 1H), 7.55 (d, J=1.0 Hz, 1H), 7.46 (s, 1H), 7.17 (d, J=8.7 Hz, 1H), 7.16 (s, 1H), 6.65 (d, J=11.5 Hz, 1H), 6.54 (d, J=8.7 Hz, 1H), 5.91(dt, J=11.5, 6.9 Hz, 1H), 3.60 (s, 3H), 2.55 (m, 2H), 2.52 (m, 2H), 2.35 (br, 8H), 2.15 (s, 3H).

^{1}H NMR of **11** (δ, DMSO-d_6): 9.90 (s, 1H), 8.62 (s, 1H), 8.34 (d, J=8.8 Hz, 1H), 7.75 (s, 1H), 7.55 (d, J=1.0 Hz, 1H), 7.51 (d, J=8.8 Hz, 1H), 7.46 (s, 1H), 7.17 (d, J=8.7 Hz, 1H), 7.16 (s, 1H), 6.54 (d, J=8.7 Hz, 1H), 5.80 (dt J=15.6, 6.6 Hz, 1H), 5.57(dt, J=15.6, 6.6 Hz, 1H), 3.61 (s, 3H), 3.57 (d, J=6.6 Hz, 2H), 2.92 (d, J=6.6 Hz, 2H), 2.35 (br, 8H), 2.15 (s, 3H).

3.3. Stille reaction: compounds 7, 10, 13–16

3.3.1. (E)-1-(Tri-n-butylstannyl)-1-buten-4-ol (*13*)

A stirred mixture of 3-butyn-1-ol (**12**) (3.50 g, 50 mmol) and AIBN (0.25 g, 1.5 mmol), contained in a round-bottomed flask equipped with a reflux condenser, was purged with N_2 at 25 °C and treated with tri-*n*-butyltin hydride (20.2 ml, 75 mmol). The mixture was slowly heated to 90 °C and the resulting vigorous exothermic reaction was moderated by removal of the heating bath and reflux of the butynol. After the initial reaction, the solution was stirred at 100 °C for 18 h. The solution was cooled and the crude product was subjected to chromatography on silica gel with a 3–20% gradient of EtOAc in hexane. After elution of a small amount of *Z*-isomer (**13**), the *E*-isomer (**14**) was obtained as a colorless oil (10.3 g, 57%). The ^{1}H NMR spectrum was identical to that reported.[24]

3.3.2. (3E)-4-(Tri-n-butylstannyl)but-3-enyl 4-methylbenzenesulfonate (*15*)

To a stirred solution of **14** (5.42 g, 15 mmol) in 30 ml of 2,6-lutidine was added tosyl chloride (8.58 g, 45 mmol) while maintaining 25 °C. After 20 h the excess tosyl chloride was decomposed by the addition of 30 ml of water and 5 ml of pyridine while cooling to maintain 25 °C. The resulting mixture was partitioned with DCM and diluted aqueous $NaHCO_3$. The organic layer was washed with water, dried, and concentrated at <35 °C, finally distilled at 0.5 mm/Hg, to give **15** (5.0 g, 65%) as an oil. ^{1}H NMR (δ, DMSO-d_6): 7.76 (d, J=8.3 Hz, 2H), 7.47 (d, J=8.3 Hz, 2H), 5.93 (d, J=18.8 Hz, 1H), 5.78 (dt, J=18.8, 5.9 Hz, 1H), 4.06 (t, J=6.5 Hz, 2H), 2.42 (s, 3H), 2.35 (m, 2H), 1.41 (m, 6H), 1.25 (m, 6H), 0.85 (m, 15H).

3.3.3. 1-Methyl-4-[(3E)-4-(tri-n-butylstannyl)but-3-enyl]piperazine (*16*)

A solution of **14** (1.55 g, 3.0 mmol), 1-methylpiperazine (1.33 ml, 12 mmol), and 3.0 ml of THF was stirred for 24 h at 25 °C and 45 °C for 2 h. The solution was concentrated to dryness under vacuum, and the residue was partitioned with 1:1 hexane/Et_2O and diluted aqueous $NaHCO_3$. The organic layer was washed with water, dried, and concentrated at <30 °C to give **16** as an amber oil (quantitative yield), which was used in the next step without purification.

3.3.4. Method B: 4-({3-chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}amino)-7-[(1E)-4-(4-methylpiperazin-1-yl)but-1-enyl]quinoline-3-carbonitrile (*10*)

A N_2-purged mixture of 7-bromo-4-{3-chloro-4-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]anilino}-3-quinolinecarbonitrile (**9**) (377 mg, 0.80 mmol), **16** (0.50 g, 1.12 mmol), and 4.0 ml of NMP were treated with $Pd(Ph_3P)_4$ (92 mg, 0.08 mmol). The mixture was stirred at 100 °C for 1 h, treated with an additional portion of $Pd(Ph_3P)_4$ (30 mg, 0.025 mmol), stirred at 110 °C for 1 h, cooled, and partitioned with DCM and diluted aqueous $NaHCO_3$. The organic layer was washed with water, dried, and concentrated. The residue was stirred in 5:1 Et_2O/hexane and the resulting solid was collected by filtration. The crude product was purified by flash column chromatography (eluting with EtOAc/MeOH/TEA) to give a solid, which was stirred in MeOH, filtered, and dried to give 251 mg (58%) of **10** as an off-white solid; mp 225 °C. MS (ESI) m/z 544.2 $(M+1)^{+1}$. Anal. Calcd for $C_{29}H_{30}ClN_7S$: C, 64.01; H, 5.56; N, 18.02. Found: C, 64.01; H, 5.52; N, 17.68.

3.3.5. 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-enyl]quinoline-3-carbonitrile (*7*)

Following the procedure used to prepare **10** (Method B), **7** was obtained from **6** and **16** as an off-white solid (65%); mp 148–150 °C. MS (ESI) m/z 526.1. Anal. Calcd for $C_{27}H_{29}Cl_2N_5O_2 \cdot 0.6H_2O$: C, 60.36; H, 5.67; N, 13.04. Found: C, 60.04; H, 5.69; N, 12.83.

3.4. Suzuki reaction: compounds 7, 10

*3.4.1. Method C: 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[(1E)-4-(4-methylpiperazin-1-yl)but-1-enyl] quinoline-3-carbonitrile (**7**)*

To a mixture of 1-but-3-ynyl-4-methyl-piperazine (**17**) (1.85 g, 14.4 mmol) and 4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**18**) (1.46 g, 9.6 mmol) was added bis(cyclopentadienyl)-zirconium chloride hydride (124 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 24 h and was diluted with toluene/ethanol/water (80 mL/8 mL/8 mL). Compound **6** (2.50 g, 4.70 mmol), K_2CO_3 (1.99 g, 14.4 mmol), and $Pd(PPh_3)_4$ (285 mg, 0.238 mmol) were added. The reaction mixture was heated at 90 °C for 4 h and partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organics were dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel flash column chromatography (10:1 CH_2Cl_2/MeOH) to give 1.92 g (75%) of **7** as an off-white solid; mp 142–143 °C. MS (ESI) *m*/*z* 526.1; ^{1}H NMR (δ, DMSO-d_6): 9.81 (br s, 1H), 8.40 (s, 1H), 7.95–7.66 (m, 3H), 7.33 (br s, 1H), 6.82 (d, *J*=16 Hz, 1H), 6.59 (m, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.49 (m, 2H), 2.50–2.30 (m, 10H), 2.18 (s, 3H); ^{13}C NMR (δ, DMSO-d_6): 154.93, 153.95, 150.15, 149.63, 142.99, 137.06, 133.89, 132.55, 129.72, 125.28, 123.88, 122.68, 120.06, 118.36, 116.84, 113.13, 101.71, 88.32, 57.29, 56.28, 54.72, 54.72, 52.51, 52.51, 45.70, 30.69, 24.93. Anal. Calcd for $C_{27}H_{29}Cl_2N_5O_2 \cdot 1.7H_2O$: C, 58.21; H, 5.84; N, 12.57. Found: C, 58.48; H, 5.47; N, 12.30.

*3.4.2. 4-({3-Chloro-4-[(1-methyl-1H-imidazol-2-yl)thio]phenyl}-amino)-7-[(1E)-4-(4-methylpiperazin-1-yl)but-1-enyl]quinoline-3-carbonitrile (**10**)*

Following the procedure used to prepare **7** (Method C), **10** was obtained from **9** as an off-white solid (63%). MS (ESI) *m*/*z* 544.2 $(M+1)^{+1}$; ^{1}H NMR (δ, DMSO-d_6): 9.86 (s, 1H), 8.59 (s, 1H), 8.30 (d, *J*=8.7 Hz, 1H), 7.80 (s, 1H), 7.79 (d, *J*=8.7 Hz, 1H), 7.54 (d, *J*=1.1 Hz, 1H), 7.44 (s, 1H), 7.16 (d, *J*=1.1 Hz, 1H), 7.15 (m, 1H), 6.64 (m, 2H), 6.54 (d, *J*=8.6 Hz, 1H), 3.61 (s, 3H), 2.37 (m, 12H), 2.15 (s, 3H); ^{13}C NMR (δ, DMSO-d_6): 152.77, 150.13, 140.95, 134.49, 132.80, 130.21, 129.90, 129.90, 129.76, 129.30, 127.92, 125.55, 125.55, 125.36, 124.08, 123.97, 123.33, 123.10, 118.37, 116.79, 88.95, 56.84, 54.11, 54.11, 51.77, 51.77, 44.94, 33.25, 29.98. Anal. Calcd for $C_{29}H_{30}ClN_7S \cdot 0.2H_2O$: C, 63.59; H, 5.59; N, 17.90. Found: C, 63.46; H, 5.57; N, 17.84.

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References and notes

1. Druker, B. J.; Talpaz, M.; Resta, D. J.; Peng, B.; Buchdunger, E.; Ford, J. M.; Lydon, N. B.; Kantarjian, H.; Capdeville, R.; Ohno-Jones, S.; Sawyers, C. L. *N. Engl. J. Med.* **2001**, *344*, 1031.
2. Deeks, E. D.; Keating, G. M. *Drugs* **2006**, *66*, 2255.
3. Shah, N. P.; Tran, C.; Lee, F. Y.; Norris, D.; Sawyers, C. L. *Science* **2004**, *305*, 399.
4. Lyseng-Williamson, K.; Jarvis, B. *Drugs* **2001**, *61*, 1765.
5. Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakatan, R.; Reich, M. F.; Shen, R.; Tsou, H. R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. *J. Med. Chem.* **2000**, *43*, 3244.
6. Boschelli, D. H. *Curr. Top. Med. Chem.* **2002**, *2*, 1051.
7. Golas, J. M.; Lucas, J.; Etienne, C.; Golas, J.; Discafani, C.; Sridhar, L.; Boghaert, E.; Arndt, K.; Ye, F.; Boschelli, D. H.; Li, F.; Titsch, C.; Huselton, C.; Chaudhary, I.; Boschelli, F. *Cancer Res.* **2005**, *65*, 5358.
8. Golas, J. M.; Arndt, K.; Etienne, C.; Lucas, J.; Nardin, D.; Gibbons, J.; Frost, P.; Ye, F.; Boschelli, D. H.; Boschelli, F. *Cancer Res.* **2003**, *62*, 375.
9. Boschelli, D. H.; Wang, Y. D.; Ye, F.; Wu, B.; Zhang, N.; Dutia, M.; Powell, D. W.; Wissner, A.; Weber, J. M.; Boschelli, F. *J. Med. Chem.* **2001**, *44*, 822.
10. Berger, D.; Dutia, M.; Powell, D.; Wu, B.; Wissner, A.; Boschelli, D. H.; Floyd, M. B.; Zhang, N.; Torres, N.; Levin, J.; Du, X.; Wojciechowicz, D.; Discafani, C.; Kohler, C.; Kim, S. C.; Feldberg, L. R.; Collins, K.; Mallon, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3031.
11. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2004**, *44*, 4442.
12. Larsen, R. D. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 651.
13. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.
14. Whitcombe, N.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449.
15. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
16. Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. Chem.* **1997**, *50*, 1.
17. Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.
18. Bellina, F.; Carpita, R. R. *Synthesis* **2004**, 2419.
19. Schmidt, A. M.; Eilbracht, P. *J. Org. Chem.* **2005**, *70*, 5528.
20. Berger, D.; Dutia, M.; Powell, D.; Wissner, A.; DeMorin, F.; Raifeld, Y.; Weber, J.; Boschelli, F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2989.
21. Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707.
22. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
23. Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahdron Lett.* **2003**, *44*, 1221.
24. Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J. *Synthesis* **2006**, *7*, 1127.
25. Boschelli, D. H.; Wang, Y.; Boschelli, F. C.; Berger, D. M.; Zhang, N.; Powell, D. W.; Ye, F.; Yamashita, A.; Demorin, F. F.; Wu, B.; Tsou, H.; Overbeek-Klumpers, E. G.; Wissner, A. U.S. Patent 6,521,618.
26. Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811.
27. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
28. Wang, Y. D.; Kimball, G.; Prashad, S. A.; Wang, Y. *Tetrahedron Lett.* **2005**, 8777.
29. Vaillancourt, V. A.; Staley, S.; Huang, A.; Nugent, R. A.; Chen, K.; Nair, S. K.; Nieman, J. A.; Strohbach, J. W. PCT Int. Appl. WO 2002002558, 2002.
30. Boschelli, D. H.; Wang, Y. D.; Johnson, S.; Wu, B.; Ye, F.; Barrios Sosa, A. C.; Golas, J. M.; Boschelli, F. *J. Med. Chem.* **2004**, *47*, 1599.
31. Berger, D. M.; Dutia, M.; Powell, D.; Floyd, M. B.; Torres, N.; Mallon, R.; Wojciechowicz, D.; Kim, S.; Feldberg, L.; Collins, K.; Chaudhary, I. *Bioorg. Med. Chem.* **2008**, *16*, 9202.