# Structure-Based Approach to the Development of Potent and Selective Inhibitors of Dihydrofolate Reductase from *Cryptosporidium*

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Cryptosporidiosis is an emerging infectious disease that can be life-threatening in an immune-compromised individual and causes gastrointestinal distress lasting up to 2 weeks in an immune-competent individual. There are few therapeutics available for effectively treating this disease. We have been exploring dihydrofolate reductase (DHFR) as a potential target in *Cryptosporidium*. On the basis of the structure of the DHFR enzyme from *C. hominis*, we have developed a novel scaffold that led to the discovery of potent (38 nM) and efficient inhibitors of this enzyme. Recently, we have advanced these inhibitors to the next stage of development. Using the structures of both the protozoal and human enzymes, we have developed inhibitors with nanomolar potency (1.1 nM) against the pathogenic enzyme and high levels (1273-fold) of selectivity over the human enzyme.

## Introduction

Cryptosporidiosis is now regarded as an emerging infectious disease,[1] and the causative agent, *Cryptosporidium hominis*, has recently been classified as a class B bioterrorism threat. Both immune-competent and immune-compromised individuals can be affected by cryptosporidiosis, usually through a contaminated water supply.[1,2] Cryptosporidiosis causes gastrointestinal distress lasting 1−2 weeks in an immune-competent individual and can be life-threatening in an immune-compromised individual, such as those with HIV, the elderly, or young children. The incidence of cryptosporidiosis continues to rise, and outbreaks are cited across the world.[3] At this time, there is a single approved therapeutic agent, nitazoxanide, against *Cryptosporidium*,[4] although the application of this drug is limited to immune-competent patients[5] and effects have not been studied in children under 12 years of age. Since the disease is more devastating and sometimes fatal to immune-compromised patients and young children, new drug discovery is critical.

We have been interested in exploring dihydrofolate reductase (DHFR[a]) as a potential drug target in *Cryptosporidium hominis* (ChDHFR). The success of DHFR inhibitors in the related Apicomplexan parasite, *Plasmodium falciparum*, the causative agent of malaria, suggests that this could be a highly effective strategy. DHFR is an essential enzyme and plays a key role in the folate biosynthetic pathway where it catalyzes the NADPH-dependent reduction of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is converted to 5,10-methylene tetrahydrofolate by serine hydroxymethyltransferase; 5,10-methylene tetrahydrofolate is a key cofactor in deoxythymidine monophosphate (dTMP) production, catalyzed by thymidylate synthase (TS).

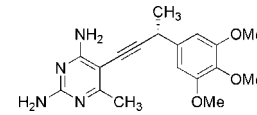


**Figure 1.** Compound **1**, a potent propargyl-based inhibitor.

In *Cryptosporidium*, DHFR and TS are present as a bifunctional enzyme, DHFR-TS (ChDHFR-TS).

Since DHFR is an essential enzyme not only to the parasite but to human cells as well, it is critical that an inhibitor be able to discriminate between the two forms of the enzymes. The difficulty of achieving both potency and selectivity for *Cryptosporidium* DHFR was underscored by a seminal study from Nelson and Rosowsky[6] in which they examined 96 structurally diverse DHFR inhibitors and were unable to identify compounds that were both potent and selective for ChDHFR. Given the difficulty of the problem, we recognized that utilization of structures of both the parasitic and human enzymes could provide us with a significant advantage in the design of effective inhibitors.

Our pursuit of a structure-based drug design approach began with the determination of crystal structures of ChDHFR-TS[7,8] to 2.7 Å resolution. With this structure in hand, we envisioned a two-stage approach to the development of effective inhibitors. In the first stage, we would focus on developing a lead series that would show high levels of potency against ChDHFR while maintaining good druglike characteristics and synthetic accessibility. On the basis of the structure of ChDHFR-TS, we developed a novel series of DHFR inhibitors defined by a propargyl linker between a 2,4-diaminopyrimidine ring and aryl ring.[9] Through these efforts, we synthesized a highly efficient ligand (Figure 1, compound **1**) with a 50% inhibition concentration ($IC_{50}$) of 38 nM and molecular weight of 342 Da. After the first stage was realized, our attention now turned to achieving high degrees of selectivity while maintaining or increasing the potency we already established. In this manuscript, we describe a series of second generation propargyl analogues inspired by structural analysis that not only maintain high levels of potency

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[a] Abbreviations: DHFR, dihydrofolate reductase; ChDHFR, dihydrofolate reductase from *Cryptosporidium hominis*; dTMP, deoxythymidine monophosphate; TS, thymidylate synthase; ChDHFR-TS, dihydrofolate reductase-thymidylate synthase from *Cryptosporidium hominis*; hDHFR, human dihydrofolate reductase; $IC_{50}$, 50% inhibition concentration; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form.

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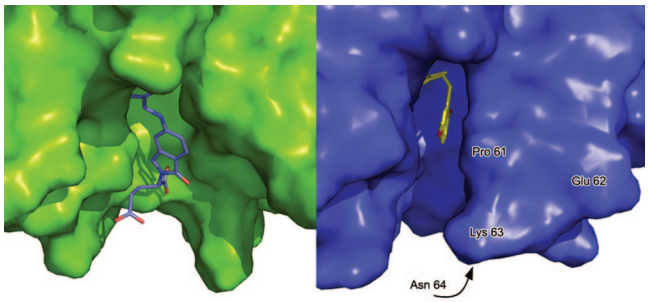



**Figure 2.** ChDHFR (green, PDB code 1SEJ) and hDHFR (blue, PDB code 1KMV) seen from the same view with cocrystallized ligands in the active site, demonstrating the substantial difference in active site opening. The PEKN loop residues are labeled on hDHFR, with Asn 64 indicated on the underside of the loop.

against the parasitic enzyme but also exhibit extremely high levels of selectivity.

## Modeling, Chemistry, and Biological Evaluation

**Structural Analysis of ChDHFR and hDHFR.** Inspection of the ChDHFR and human DHFR (hDHFR) structures reveals that the active sites are highly homologous and residue differences that exist maintain the same chemical properties. The most striking difference between these two enzymes is located at the opening to the active site. In hDHFR, access to the active site is effectively restricted by a four-residue loop (Pro 61, Glu 62, Lys 63, Asn 64; or PEKN loop) that is notably absent in ChDHFR (Figure 2).[7] We envisioned that this structural difference could be exploited to design ligands with selectivity for ChDHFR.

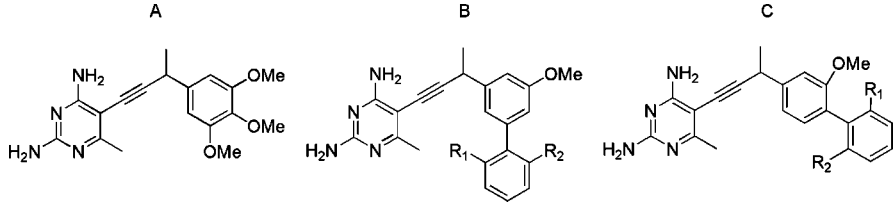
Initial docking analysis with our first generation propargyl inhibitors showed that our lead compound **1** did not appear to exploit these differences. Indeed, **1** showed only a modest 36-fold preference for the parasitic enzyme over the human enzyme (Table 1). It was therefore obvious that additional elements would need to be incorporated into the initial lead structure to develop a highly selective compound.

Inspection of docked complexes of the lead in ChDHFR and hDHFR suggested that functionality projecting from the meta or para position on the aromatic core of **1** would be correctly poised to interact with a region of space filled by the PEKN loop in hDHFR (Scheme 1). Accordingly, we could tune the steric interaction to destabilize binding to the human enzyme while maintaining high potency against the protozoal form. Clearly, the extent of these interactions would be highly dependent on the degree of rigidity in this PEKN loop region. Supporting the idea that the loop is rigid, a solution structure of hDHFR determined by NMR shows little variance in this region.[10] The newly designed analogues (**2** and **3**) maintained three moieties: (1) the methyl at C6 of the pyrimidine, which is predicted to interact with Phe 36, Leu 33, and Leu 25; (2) the propargyl methyl, which is predicted to interact favorably with residues Thr 58 and Ile 62 and Cys 113; and (3) the 3′ methoxy group, predicted to interact with both the backbone and side chain of Leu 25 in the active site.[9]

A direct method for introducing steric bulk onto the aromatic core region was required for synthesis of the second generation inhibitors. These considerations led us to consider a biaryl type of scaffold where the steric bulk would be introduced in the form of an additional aromatic ring. The selection of such a scaffold allowed us to take advantage of the flexibility and versatility offered by Suzuki cross-coupling for the preparation of a wide range of potential inhibitors.

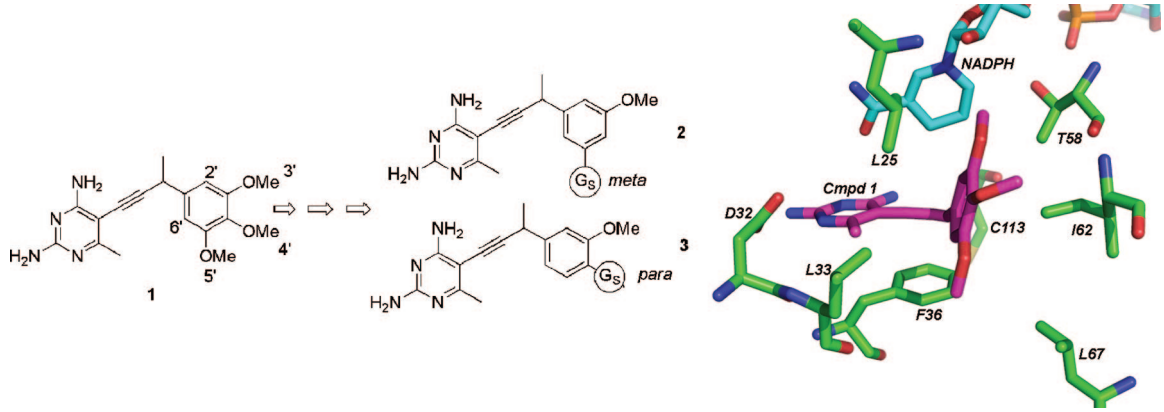
The two analogue families based on compounds **2** and **3** with variable substitution patterns on the distal aryl ring were created virtually and docked into both ChDHFR and hDHFR using the program Surflex (Tripos) in the Sybyl environment. Surflex flexibly docks ligands to a protomol representation of the active site, created by probing the active site with small molecular fragments. Ligands are fragmented and built into the protomol based on an empirical scoring function that includes hydrophobic, polar, repulsive, entropic, and solvation terms. In order to explore protein flexibility, ensembles of receptor structures were created on the basis of minimized conformational snapshots across a molecular dynamics time course. While there are several methods to generate an averaged score for a given ensemble such as weighting docking scores or conformational energy using a Boltzmann distribution, using *K**, a Boltzmann-weighted partition function,[11] or selecting ensemble members a priori based on pharmacophoric restraints,[12] we chose to use simple arithmetic averaging for this study. Arithmetically averaging docking scores from the ensemble provided a means to simply, effectively and equally, weight complexes over a narrow energy

**Table 1.** Inhibitory Potency and Selectivity of DHFR Ligands ($IC_{50}$ Values in nM)



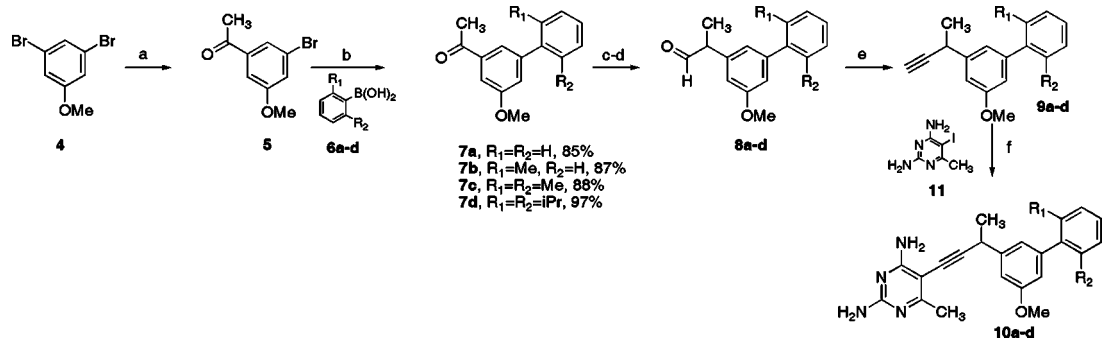

| compd | scaffold | $R_1$ | $R_2$ | $IC_{50}$ (nM) ChDHFR | hDHFR | selectivity ratio $IC_{50}$(ChDHFR)/($IC_{50}$)hDHFR |
|---|---|---|---|---|---|---|
| *R*-**1** | A | | | 38 ± 1 | 1380 ± 20 | 36 |
| **10a** (±) | B | H | H | 1.8 ± 0.2 | 1700 ± 10 | 944 |
| **10b** (±) | B | H | $CH_3$ | 2.1 ± 0.3 | 1360 ± 50 | 648 |
| **10c** (±) | B | $CH_3$ | $CH_3$ | 2.1 ± 0.5 | 1250 ± 6 | 595 |
| **10d** (±) | B | *i*-Pr | *i*-Pr | 10 ± 2 | 7200 ± 150 | 720 |
| **17a** (±) | C | H | H | 19 ± 3 | 1420 ± 12 | 75 |
| **17b** (±) | C | H | $CH_3$ | 36 ± 0.6 | 2770 ± 59 | 77 |
| **17c** (±) | C | $CH_3$ | $CH_3$ | 7.4 ± 1.9 | 3370 ± 15 | 455 |
| **17d** (±) | C | *i*-Pr | *i*-Pr | 16 ± 2 | 4200 ± 0.1 | 262 |
| *R*-**10a** | B | H | H | 1.1 ± 0.1 | 1360 ± 26 | 1273 |
| *S*-**10a** | B | H | H | 30 ± 1.5 | 1380 ± 26 | 46 |

**Scheme 1.** Overall Strategy for Adding Steric Substitutions to the Meta or Para Position of the Initial Lead Compound[a]




[a] $G_S$ is a sterically bulky group. The docked complex of compound **1** (magenta) is bound to the active site of ChDHFR (green).

**Scheme 2.** Synthesis of Meta-Linked Biphenyl Inhibitors[a]




[a] (a) *n*-BuLi, −78 °C, then $CH_3C(O)N(CH_3)_2$, 71%; (b) $Pd(PPh_3)_2Cl_2$, $Cs_2CO_3$, dioxane; (c) $Ph_3P{=}CHOMe$, THF; (d) concentrated HCl, THF, reflux, 57−82% for two steps; (e) dimethyl (1-diazo-2-oxopropyl)phosphonate, $K_2CO_3$, MeOH, 64−99%; (f) $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, DMF, 67−94%.

range. Docking scores are returned with an associated "crash value" that largely approximates the penetration of the ligand into the receptor (values for crash that are closer to 0 are preferred). Because we are attempting to exploit a steric interaction, the crash value score within Surflex appeared as an attractive metric to evaluate these inhibitors.

By employment of these computational methods, a series of eight potential inhibitors was selected. Four of the inhibitors were in the meta series of inhibitors, and four were in the para series (see Scheme 1). Each series comprised derivatives that incorporated increasing steric bulk at the ortho positions of the distal aryl ring. The ortho positions were chosen for substitution to ensure that the two aryl rings are not coplanar, thus increasing the steric bulk. The computational analysis predicted that the crash values against hDHFR for these inhibitors became increasingly negative as the steric volume of the distal aryl ring increased with minimal change in ChDHFR. For example, a compound with an unsubstituted aryl ring yielded a crash value of −1.31 in ChDHFR and −2.79 in hDHFR. An analogous compound with isopropyl groups in both ortho positions yielded increased crash values of −4.08 and −12.76 in ChDHFR and hDHFR, respectively. On the basis of these predictors, we were confident that this new series of inhibitors was effectively exploring differences between these two enzymes.

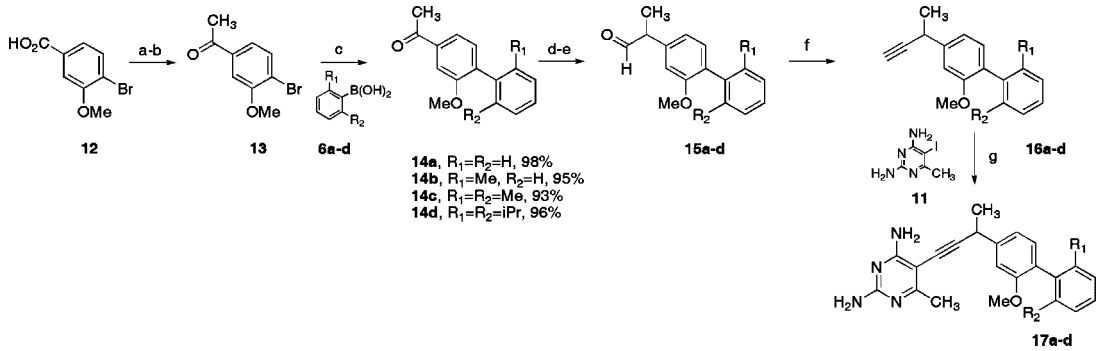
**Synthesis.** We developed a modular and flexible approach to these inhibitors by relying on two subsequent palladium-catalyzed coupling reactions. The meta-linked biphenyl analogues were accessed by selective functionalization of commercially available 3,5-dibromoanisole **4** (Scheme 2).

Metal−halogen exchange followed by addition of *N*,*N*-dimethylacetamide gave the acetophenone derivative **5**, which was cross-coupled with the four arylboronic acids **6a**−**d** to give the corresponding biphenyl derivatives **7a**−**d**. The diisopropylboronic acid **6d** was not previously known but was easily prepared from 2,6-diisopropylaniline by diazotization, iodination, and final conversion to the boronic acid via lithiation/boronation (see Supporting Information). Homologation of the acetyl moiety by condensation with a methoxy substituted phosphorus ylide and hydrolysis of the resulting enolether gave aldehydes **8a**−**d** in very good yield. Condensation with the Ohira−Bestmann reagent gave the corresponding terminal acetylenes **9a**−**d** that were converted to the inhibitors **10a**−**d** by a final Sonogashira coupling with iodopyrimidine **11**.

The para-linked biphenyl analogues were accessed through a similar route from the commercially available benzoic acid derivative **12** (Scheme 3). Conversion of the acid to the acyl chloride and treatment of the crude material with the Gilman reagent produced an excellent yield of the acetophenone **13**. Suzuki cross-coupling proceeded as before with high levels of efficiency to give the key biphenyl intermediates **14a**−**d**. The acetyl group was homologated through a series of identical reactions as outlined previously to arrive at the inhibitor series **17a**−**d**.

The eight inhibitors produced by the routes outlined in Schemes 2 and 3 are racemic with regard to the stereogenic center at the propargylic carbon. Upon evaluation of these compounds (see below) we selected the most selective racemic inhibitor, **10a**, and generated both enantiomers to probe the stereochemical impact of this center upon affinity and selectivity. This asymmetric route is analogous to the one described previously[9] for the generation of enantiopure **1** and relies on

**Scheme 3.** Synthesis of Para-Linked Biphenyl Inhibitors[a]




[a] (a) $(COCl)_2$, cat. DMF, $CH_2Cl_2$; (b) $Li(CH_3)_2Cu$, THF, 90% for two steps; (c) $Pd(PPh_3)_2Cl_2$, $Cs_2CO_3$, dioxane; (d) $Ph_3P{=}CHOMe$, THF; (e) concentrated HCl, THF, reflux, 80−92% for two steps; (f) dimethyl (1-diazo-2-oxopropyl)phosphonate, $K_2CO_3$, MeOH, 51−75%; (g) $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, DMF, 53−97%.

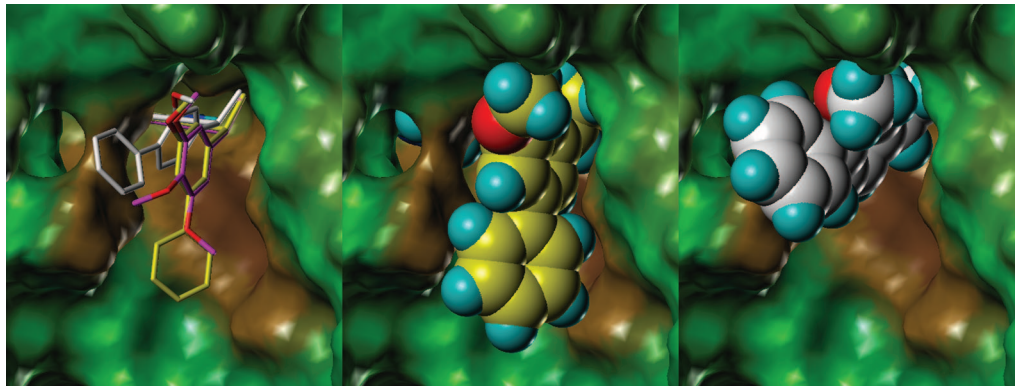


**Figure 3.** Compounds **1** (pink), **10a** (yellow), and **17a** (white) docked into ChDHFR in their computationally preferred orientations. ChDHFR is shown as a surface mapped with lipophilicity in a gradient from lipophilic (red) to neutral (green) to hydrophilic (blue).

the use of an Evans' asymmetric alkylation strategy to set the single stereogenic center in the inhibitor (Scheme 4).

Lithiation of dibromoanisole **4** as previously described, followed by condensation with dimethylformamide and a subsequent Suzuki coupling, gave biphenylaldehyde **18** in excellent overall yield. The aldehyde was homologated through the intermediacy of an enol ether and subsequently oxidized to produce the arylacetic acid **19**. The acid was converted to the two enantiomerically pure oxazolidinones **20** and **21** under standard conditions. Methylation of the derived enolates proceeded with high levels of diastereoselection to give oxazolidinones **22** and **23**. These compounds were converted to the dibromoalkenes **24** and **25** through a three-step sequence of reduction, oxidation, and olefination without purification of the intermediate aldehyde. Treatment of the dibromoalkenes with elemental magnesium delivered the terminal alkynes in excellent yield. The two enantiomerically pure (greater than 97% ee) inhibitors *R*-**10a** and *S*-**10a** were prepared by a final cross-coupling reaction.

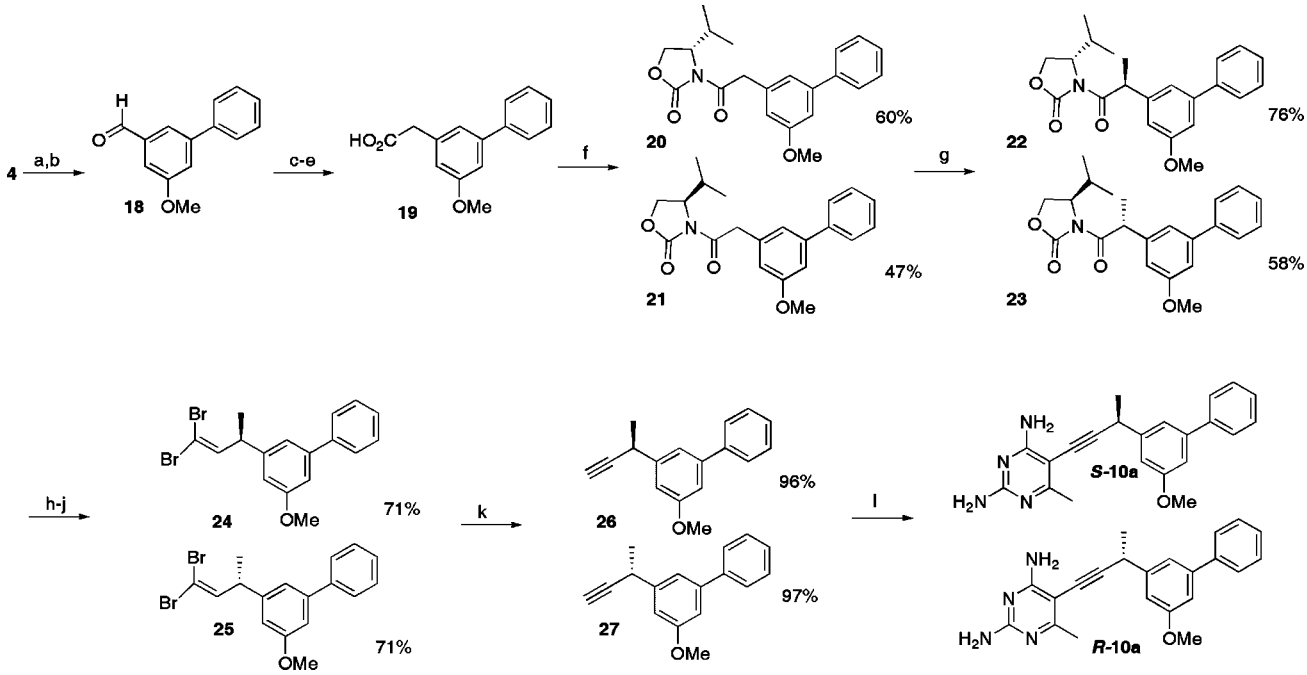
**Biological Evaluation.** All compounds were evaluated in spectrophotometric enzyme inhibition assays using ChDHFR-TS and hDHFR. Inhibition concentrations ($IC_{50}$) were measured and are reported in Table 1. The lead compound, **1**, has an $IC_{50}$ value of 38 nM and modest selectivity (36-fold). All of the biphenyl compounds are more potent than the initial lead compound, **1**, and exhibit greater selectivity for the pathogenic enzyme. The most potent racemic compound, **10a**, a *m*-biphenyl derivative, is also the most selective of the racemic compounds (944-fold). To our knowledge, the single *R* enantiomer of this *m*-biphenyl analogue is the most potent (1.1 nM) and most selective (1273-fold) of all known compounds tested against the *Cryptosporidium* DHFR enzyme.

## Discussion

Here, we report the design and synthesis of very potent and selective inhibitors of the *Cryptosporidium* DHFR enzyme. Our initial lead compound, **1**, exhibited good potency (38 nM) but only modest selectivity (36-fold) toward the pathogenic enzyme. Examination of the structures of ChDHFR and hDHFR led us to explore two biphenyl series of derivatives in which the second aryl ring was installed at the meta or para position of the proximal aryl ring. Computational analysis of these series led to the synthesis of 10 new inhibitors, all of which exhibit improved potency and selectivity. The racemic *m*-biphenyl analogue **10a** was the most potent and selective of the racemic compounds, with the single *R* enantiomer (*R*-**10a**) being the most potent and selective compound overall.

Inspection of the inhibition assay data in Table 1 shows several important relationships. Relative to compound **1**, all of the newly synthesized inhibitors display increased potency against ChDHFR while showing similar or slightly lower activity against the human enzyme, driving the increase in selectivity. Within the two series there are additional trends. The meta series is generally more potent than the para series for both enzymes. The effect of increasing methylation on the distal ring seems negligible for the meta series in both enzymes but does appear to decrease affinity in the para series for hDHFR. The more sterically demanding isopropyl substitution significantly lowers affinity in all cases. In order to re-evaluate our original hypothesis, we returned to computational modeling.

**Scheme 4.** Synthesis of Nonracemic DHFR Inhibitors[a]




[a] (a) *n*-BuLi, −78 °C, then DMF, 98%; (b) $Pd(PPh_3)_2Cl_2$, $Cs_2CO_3$, dioxane, 82%; (c) $Ph_3P{=}CHOMe$, THF; (d) concentrated HCl, THF, reflux; (e) Jones reagent, 72% for three steps; (f) $(CH_3)_3CCOCl$, $Et_3N$, then lithiooxazolidinone; (g) LHMDS, then MeI; (h) $LiAlH_4$, THF; (i) Dess−Martin periodinane, $CH_2Cl_2$; (j) $CBr_4$, $PPh_3$; (k) Mg, THF; (l) iodopyrimidine (**11**), $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, DMF, 93−97%.

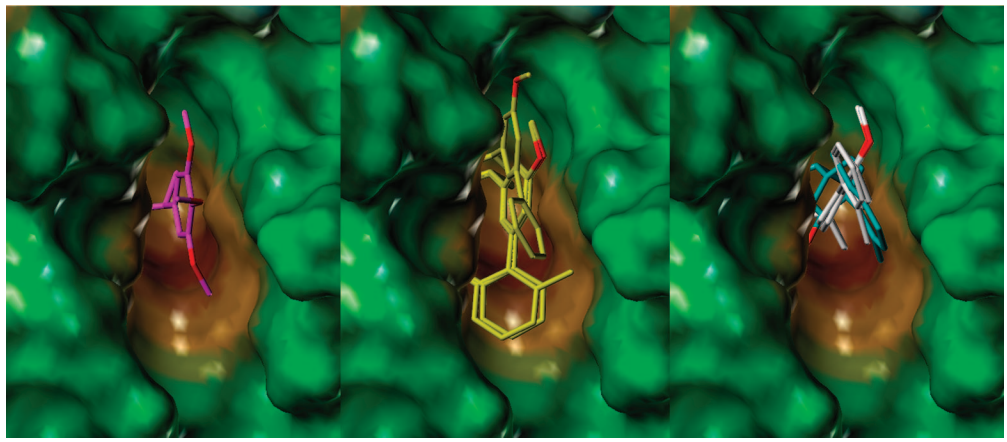


**Figure 4.** Compounds **1** (pink), **10a**−**c** (yellow), and **17a**−**c** docked into the hDHFR ensemble member with the widest opening. hDHFR surface is colored based on a lipophilicity gradient from lipophilic (red) to neutral (green) to hydrophilic (blue).

**Analysis of the Interactions of the Biphenyl Compounds with ChDHFR.** The docked conformations of both the meta and para series of biphenyl compounds appear to increase lipophilic contacts between the ligand and ChDHFR active site relative to those observed with compound **1**. Computational analysis of the compounds docked into ChDHFR also explains the clear preference for the meta-substituted compounds as opposed to the para-substituted compounds. With the 3′-OMe anchored in a small hydrophobic pocket, the distal phenyl ring is projected toward the lipophilic opening of the active site in the meta series, generating favorable contacts. In contrast, in the para series, the distal ring is projected directly out of the active site into solution, thus providing minimal ChDHFR contacts (Figure 3).

**Analysis of the Interactions of the Biphenyl Compounds with hDHFR.** Although our initial computational studies predicted that both the meta and para series would display decreased affinity for hDHFR, only the para series followed this trend. In order to better understand the divergent trend between these two families, we conducted a similar detailed analysis with the human enzyme.

As shown in Figure 4, the active site opening in hDHFR is substantially narrower and less lipophilic than in ChDHFR. The PEKN loop projects perpendicularly from the wall of the active site, creating a cleft below the loop. Our initial modeling suggested that substitutions on the distal ring would produce unfavorable interactions in this region. However, evaluation of the compounds shows that inclusion of the second ring did little to change the potency of compound **1**. We have attributed this discrepancy to a greater degree of flexibility in this loop than originally anticipated. This increased flexibility may allow the meta series of compounds to access the cleft below the loop in a more productive manner, thus compensating for some of the destabilizing interactions introduced by the second ring. In the larger isopropyl compound, **10d**, there does not appear to be enough flexibility to compensate.

In contrast, the para series of compounds project into an alternative pocket that is severely hindered by the PEKN loop and the opposing wall of the active site. As expected, increased steric volume occupied by the distal aryl ring directly correlates with a decrease in affinity.

In conclusion, these studies demonstrate that taking advantage of small differences between these enzymes combined with detailed structural analysis provides a significant advantage in the design of more efficacious inhibitors. Utilizing the structural information, we have been able to increase the selectivity of a lead compound from 36-fold to 1273-fold (a 35-fold gain) with a concomitant 35-fold improvement in affinity for the target enzyme while synthesizing only 10 new analogues.

## Experimental Section

**Enzyme Expression, Purification, and Assays.** ChDHFR-TS was expressed in *E. coli* and purified using a methotrexate agarose column.[9] The gene for hDHFR was amplified using PCR from cDNA obtained from ATCC. The gene was inserted in a pET41 vector with a C-terminal histidine tag for affinity chromatography. The resulting construct was verified by sequencing. The hDHFR protein was expressed in *E. coli* and purified using a nickel affinity column. Enzyme activity assays were performed by monitoring the change in UV absorbance at 340 nm as previously described.[9] Enzyme assays were performed at least four times. $IC_{50}$ values and their standard deviations were calculated in the presence of varying ligand concentration.

**Computational Modeling.** All ligands were drawn in Sybyl[13] in an analogous fashion to make the starting conformations as similar as possible. Ligands were then brought to their local energy minima using the Tripos force field. The resulting structures were checked for proper geometries and selectively protonated at N1 of the 2,4-diaminopyrimidine ring.

Ensembles of receptors were used to model protein flexibility. Receptors were prepared by adding hydrogens, removing waters, and calculating formal charges. Ensemble sets were created by taking 500 fs conformational snapshots across a 10 000 fs molecular dynamics run at 300 K using the Amber force field in Sybyl. All structures were then brought to their local energy minima with a 1000 iteration energy change gradient, under the assumption that high-energy conformations are not likely to be biologically active. Mobility was limited to a specific active site, as defined by all atoms falling within a sphere of a specific radius around the cocrystallized ligand. For ChDHFR, the structure 1SEJ[7] was used with a 6 Å sphere around the tricyclic core of the ligand defining the active site. 1KMV[14] was used as the hDHFR structure. The unresolved sidechains of Asp 21 and Lys 62 were constructed using the most common side chain angles from a Lovell dictionary.[15] Motion of 1KMV was confined to a 6 Å sphere around the ligand and PEKN loop region residues 59−68. The conserved acidic residue (Glu 30) was held rigid throughout the MD to preserve the essential N1H hydrogen bonding contact. It was not necessary to hold the conserved acidic residue rigid in the case of ChDHFR, as the contact was preserved across the time course.

Docking was carried out using Surflex-Dock[16] as implemented by Sybyl 7.3. Surflex-Dock includes a solvation function that captures the difference between the potential and actual numbers of hydrogen bond equivalents. An in-house script was used to dock against ensembles of receptors. Because of the conserved orientation of the 2,4-diaminopyrimidine moiety in the active site, the correct placement of the ligand could be determined. The top scoring poses with the conserved orientation, the N1H located within hydrogen bond distance of the conserved acidic residue, and the C2 $NH_2$ located within 4.3 Å of the conserved Thr oxygen were analyzed. Scores were averaged across the ensemble because we have previously determined this to be the most effective.[17]

**Synthesis. General.** The $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker instruments at 500 and 125 MHz or 300 and 75 MHz, respectively. Chemical shifts are reported in ppm and are referenced to residual $CHCl_3$ solvent; 7.26 and 77.0 ppm for $^1H$ and $^{13}C$, respectively. Melting points were recorded on Mel-Temp 3.0 apparatus and are uncorrected. High-resolution mass spectrometry was provided by the Notre Dame Mass Spectrometry Laboratory. IR data were obtained using a Shimadzu 8400-s FTIR spectrometer. TLC analyses were performed on Whatman Partisil K6F silica gel 60 plates. All glassware was oven-dried and allowed to cool under an argon atmosphere. Anhydrous dichlormethane, ether, and tetrahydrofuran were used directly from Baker cycletainers. Anhydrous dimethylformamide was purchased from Acros and degassed by purging with argon. Anhydrous triethylamine was purchased from Aldrich and degassed by purging with argon. All reagents were used directly from commercial sources unless otherwise stated. Boronic acids **6a**−**c** were purchased from Aldrich. Boronic acid **6d** was synthesized in two steps from commercial 2,6-diisopropylaniline (see Supporting Information). The Ohira−Bestmann reagent[18] and Dess−Martin periodinane[19] were synthesized according to literature procedures. Dibromoanisole **4** was purchased from Aldrich or synthesized from commercially available 1,3,5-tribromobenzene.[20] 2,4-Diamino-5-iodo-6-methylpyrimidine **11** was synthesized according to literature procedures.[9]

**1-(3-Bromo-5-methoxyphenyl)ethanone (5).** To a −78 °C solution of *n*-BuLi (1.75 M in hexanes, 10.75 mL, 18.8 mmol) in dry THF (24 mL) under argon was added a solution of dibromide **4** (5.0 g, 18.8 mmol) in dry THF (15 mL) dropwise. White solids formed, and the mixture was stirred for 20 min at −78 °C. Then anhydrous dimethylacetamide (1.92 mL, 20.7 mmol) was added slowly over ∼10 min. After the mixture was stirred an additional 20 min at −78 °C, the reaction was quenched with 30 mL of 1 M HCl and the mixture was warmed to ambient temperature. The mixture was diluted with ether (30 mL) and the organic phase separated. The aqueous phase was extracted with ether (2 × 20 mL), and the combined extracts were washed with saturated $NaHCO_3$ and brine (30 mL each), dried over sodium sulfate, and concentrated. The crude oil was purified by flash chromatography (100 g $SiO_2$, 5% EtOAc/hexanes) to provide ketone **5** as a white solid (3.06 g, 71%): TLC $R_f$ = 0.19 (5% EtOAc/hexanes); mp 39.1−39.7 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.62 (m, 1H), 7.38 (dd, $J$ = 2.4, 1.4 Hz, 1H), 7.22 (dd, $J$ = 2.4, 1.7 Hz, 1H), 3.83 (s, 3H), 2.56 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 196.3, 160.4, 139.5, 123.9, 123.0, 122.0, 112.0, 55.7, 26.6; IR (neat, KBr, $cm^{-1}$) 3084, 2939, 2837, 1693, 1454, 1277, 1043, 739; HRMS (FAB, $MH^+$) $m/z$ 228.9881 (calculated for $C_9H_{10}BrO_2$, 228.9864).

**General Procedure for the Suzuki Coupling: 1-(3-Methoxy-5-(2,6-dimethylphenyl)phenyl)ethanone (7c).** To a 15 mL screw cap pressure vessel was added ketone **5** (0.517 g, 2.26 mmol), 2,6-dimethylphenylboronic acid **6c** (0.680 g, 4.53 mmol), $Cs_2CO_3$ (2.20 g, 6.75 mmol), $Pd(PPh_3)_2Cl_2$ (0.150 g, 0.21 mmol, 9% Pd), and anhydrous dioxane (4.5 mL). The mixture was stirred and then degassed once using the freeze/pump/thaw method. Once the mixture warmed to room temperature, the vessel was sealed under argon and placed in an 80 °C oil bath for 14 h (overnight). An aliquot was analyzed by $^1H$ NMR to confirm the disappearance of starting material (loss of $-OCH_3$ singlet). The dark colored mixture was cooled, diluted with ether (8 mL), and filtered through a pad of silica gel (∼15 g), rinsing with ether. The filtrate was concentrated and the residue purified by flash chromatography ($SiO_2$ 25 g, 2−5% EtOAc/hexanes) to afford biphenyl ketone **7c** as a white solid (0.505 g, 88%): TLC $R_f$ = 0.17 (5% EtOAc/hexanes); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.49 (dd, $J$ = 2.5, 1.5 Hz, 1H), 7.35 (m, 1H), 7.20 (m, 1H), 7.13 (m, 2H), 6.94 (dd, 2.5, 1.4 Hz, 1H), 3.89 (s, 3H), 2.60 (s, 3H), 2.06 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.9, 160.0, 142.8, 140.6, 138.7, 135.8, 127.5, 127.4, 122.0, 120.3, 110.6, 55.5, 26.8, 20.7; IR (neat, KBr, $cm^{-1}$); HRMS (FAB, $M^+$) $m/z$ 254.1315 (calculated for $C_{17}H_{18}O_2$, 254.1307).

**1-(3-Methoxy-5-phenyl)phenylethanone (7a).** According to the general Suzuki coupling procedure, ketone **5** (0.343 g, 1.5 mmol) was reacted with phenylboronic acid **6a** (0.366 g, 3.0 mmol), $Cs_2CO_3$ (1.48 g, 4.54 mmol), and $Pd(PPh_3)_2Cl_2$ (0.044 g, 0.063 mmol, 4% Pd) in 3 mL of dioxane for 2 h. Following the general reaction workup, flash chromatography ($SiO_2$ 25 g, 5% EtOAc/

hexanes) afforded biphenyl ketone **7a** as a clear oil (0.287 g, 85%): TLC $R_f = 0.20$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.76 (t, $J = 1.5$ Hz, 1H), 7.60 (m, 2H), 7.50−7.42 (m, 3H), 7.38 (m, 1H), 7.32 (dd, $J = 2.5$, 1.5 Hz, 1H), 3.90 (s, 3H), 2.64 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 160.1, 142.9, 140.0, 138.8, 128.8, 127.8 127.1, 119.9, 118.1, 111.2, 55.4, 26.7; IR (neat, KBr, $cm^{-1}$) 3082, 2939, 1684, 1591, 1358, 1211, 1045, 763; HRMS (FAB, $MH^+$) *m/z* 227.1078 (calculated for $C_{15}H_{15}O_2$, 227.1072).

**1-(3-Methoxy-5-(2-methylphenyl)phenyl)ethanone (7b).** According to the general Suzuki coupling procedure, ketone **5** (0.175 g, 0.764 mmol) was reacted with 2-methylphenylboronic acid **6b** (0.207 g, 1.52 mmol), $Cs_2CO_3$ (0.750 g, 2.30 mmol), and $Pd(PPh_3)_2Cl_2$ (0.054 g, 0.076 mmol, 10% Pd) in 1.5 mL of dioxane for 4.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 7 g, 2−5% EtOAc/hexanes) afforded biphenyl ketone **7b** as a clear oil (0.159 g, 87%): TLC $R_f = 0.14$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (m, 2H), 7.32 − 7.22 (m, 4H), 7.09 (dd, $J = 2.5$, 1.4 Hz, 1H), 3.90 (s, 3H), 2.62 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.0, 159.6, 143.6, 140.7, 138.3, 135.2, 130.4, 129.5, 127.7, 125.9, 122.1, 120.3, 110.8, 55.5, 26.8, 20.3; IR (neat, KBr, $cm^{-1}$) 3003, 2957, 1686, 1589, 1333, 1229, 762; HRMS (FAB, $M^+$) *m/z* 240.1154 (calculated for $C_{16}H_{16}O_2$, 240.1150).

**1-(3-(2,6-Diisopropylphenyl)-5-methoxyphenyl)ethanone (7d).** According to the general Suzuki coupling procedure, ketone **5** (0.251 g, 1.09 mmol) was reacted with boronic acid **6d** (0.450 g, 2.18 mmol), $Cs_2CO_3$ (1.07 g, 3.28 mmol), and $Pd(PPh_3)_2Cl_2$ (0.039 g, 0.056 mmol, 5% Pd) in 2 mL of dioxane for 14.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 12 g, 2% EtOAc/hexanes) afforded biphenyl ketone **7d** as a clear, viscous oil (0.331 g, 97%): TLC $R_f = 0.19$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.52 (dd, $J = 2.5$, 1.5 Hz, 1H), 7.39 (m, 2H), 7.24 (d, $J = 7.8$ Hz, 2H), 6.98 (dd, $J = 2.5$, 1.3 Hz, 1H), 3.90 (s, 3H), 2.61 (sep, $J = 6.9$ Hz, 2H), 2.60 (s, 3H), 1.12 (d, $J = 6.9$ Hz, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 197.9, 159.5, 146.6, 142.3, 138.14, 138.09, 128.2, 122.7, 122.5, 120.8, 110.4, 55.5, 30.2, 26.8, 24.2, 24.1; IR (neat, KBr, $cm^{-1}$) 3065, 2962, 1688, 1585, 1360, 1204, 735; HRMS (FAB, $M^+$) *m/z* 310.1937 (calculated for $C_{21}H_{26}O_2$, 310.1933).

**General Procedure for the Wittig Homologation/Enol Ether Hydrolysis: 2-(3-Methoxy-5-(2,6-dimethylphenyl)phenyl)propanal (8c).** To a 0 °C suspension of methoxymethyltriphenylphosphonium chloride (0.758 g, 2.21 mmol) in dry THF (6 mL) under an argon atmosphere was added NaO$^t$Bu (0.260 g, 2.70 mmol) in one portion. The red-orange suspension was stirred for a further 0.5 h at 0 °C. Then a solution of biphenyl ketone **7c** (0.284 g, 1.12 mmol) in THF (1 mL) was added dropwise. Following 20 min, the reaction was quenched with water (15 mL) and diluted with ether (15 mL). The organic phase was separated and the aqueous phase extracted with additional ether (2 × 10 mL). The combined extracts were washed with brine (15 mL), dried over sodium sulfate, and concentrated to afford the crude product that was filtered through a column of silica ($SiO_2$ 21 g, 1% EtOAc/hexanes) to afford 0.288 g of a mixture of enol ethers ($E/Z \approx 60{:}40$) that were immediately hydrolyzed in the subsequent step: TLC $R_f = 0.50$ (5% EtOAc/hexanes).

To a solution of enol ether (0.288 g, 1.02 mmol) in THF (6 mL) was added concentrated HCl (0.4 mL). The solution was warmed in an oil bath to between 55 and 65 °C and monitored by TLC. Once the starting material had been consumed (∼1 h), the mixture was cooled and diluted with water and ether (15 mL each). The organic phase was separated and the aqueous phase extracted with additional ether (2 × 15 mL). The combined extracts were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over sodium sulfate, and concentrated to afford the crude product that was purified by flash chromatography ($SiO_2$ 11 g, 2−5% EtOAc/hexanes) to afford aldehyde **8c** as a colorless oil (0.248 g, 82% from **7c**): TLC $R_f = 0.26$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.72 (d, $J = 1.4$ Hz, 1H), 7.18 (m, 1H), 7.11 (m, 2H), 6.74 (m, 1H), 6.66 (m, 1H), 6.62 (m, 1H), 3.83 (s, 3H), 3.64 (dq, $J = 7.1$, 1.4 Hz, 1H), 2.06 (s, 6H), 1.47 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.8, 160.2, 143.2, 141.2, 139.3, 135.8, 127.3, 127.2, 121.3, 113.4, 112.3, 55.3, 52.9, 20.7. 14.5; IR (neat, KBr, $cm^{-1}$) 3063, 2974, 2716, 1722, 1589, 1458, 1207, 1029, 773; HRMS (FAB, $M^+$) *m/z* 268.1466 (calculated for $C_{18}H_{20}O_2$, 268.1463).

**2-(3-Methoxy-5-phenylphenyl)propanal (8a).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (0.76 g, 2.2 mmol), NaO$^t$Bu (0.279 g, 2.9 mmol) and biphenyl ketone **7a** (0.287 g, 1.3 mmol) gave, following filtration ($SiO_2$ 27 g, 2% EtOAc/hexanes), 0.267 g of a mixture ($E/Z \approx 55{:}45$) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f = 0.43$ (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.265 g) was reacted with concentrated HCl (0.5 mL) in THF (10 mL) for 1 h. Following the general reaction workup, flash chromatography ($SiO_2$ 15 g, 5% EtOAc/hexanes) afforded aldehyde **8a** as a clear oil (0.187 g, 61% from **7a**): TLC $R_f = 0.20$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.74 (m, 1H), 7.60 (m, 2H), 7.46 (m, 2H), 7.38 (m, 1H), 7.09 (m, 1H), 7.04 (m, 1H), 6.76 (m, 1H), 3.88 (s, 3H), 3.68 (m, 1H), 1.5 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 200.7, 160.4, 143.5, 140.6, 139.5, 128.7, 127.6, 127.1, 119.6, 112.8, 111.8, 55.3, 53.1, 14.5; IR (neat, KBr, $cm^{-1}$) 2974, 2717, 1720, 1593, 1213, 1053; HRMS (FAB, $M^+$) *m/z* 240.1158 (calculated for $C_{16}H_{16}O_2$, 240.1150).

**2-(3-Methoxy-5-(2-methylphenyl)phenyl)propanal (8b).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (1.10 g, 3.21 mmol), NaO$^t$Bu (0.432 g, 4.5 mmol) and biphenyl ketone **7b** (0.540 g, 2.25 mmol) gave, following filtration ($SiO_2$ 25 g, 1% EtOAc/hexanes), 0.383 g of a mixture ($E/Z \approx 60{:}40$) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f = 0.44$ (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.383 g) was reacted with concentrated HCl (0.5 mL) in THF (8 mL) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 12 g, 2−5% EtOAc/hexanes) afforded aldehyde **8b** as a clear oil (0.327 g, 57% from **7b**): TLC $R_f = 0.19$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.75 (d, $J = 1.4$ Hz, 1H), 7.32−7.24 (m, 4H), 6.85 (m, 1H), 6.80 (m, 1H), 6.77 (m, 1H), 3.86 (s, 3H), 3.67 (dq, $J = 7.0$, 1.4 Hz, 1H), 2.31 (s, 3H), 1.50 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.7, 159.8, 144.0, 141.3, 138.8, 135.1, 130.3, 129.5, 127.5, 125.7, 121.6, 113.7, 112.5, 55.2, 52.9, 20.3, 14.4; IR (neat, KBr, $cm^{-1}$) 3059, 2934, 2716, 1724, 1591, 1456, 1213, 1030, 761; HRMS (FAB, $M^+$) *m/z* 254.1312 (calculated for $C_{17}H_{18}O_2$, 254.1307).

**2-(3-Methoxy-5-(2,6-diisopropylphenyl)phenyl)propanal (8d).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (0.683 g, 2.0 mmol), NaO$^t$Bu (0.248 g, 2.6 mmol), and biphenyl ketone **7d** (0.354 g, 1.14 mmol) gave, following filtration ($SiO_2$ 20 g, 1% EtOAc/hexanes), 0.364 g of crude material that was immediately hydrolyzed in the subsequent step: TLC $R_f = 0.42$ (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.364 g) was reacted with concentrated HCl (0.5 mL) in THF (8 mL) for 2 h. Following the general reaction workup, flash chromatography ($SiO_2$ 18 g, 2−5% EtOAc/hexanes) afforded aldehyde **8d** as a clear oil (0.272 g, 73% from **7d**): TLC $R_f = 0.26$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.76 (d, $J = 1.4$ Hz, 1H), 7.39 (m, 1H), 7.26 (d, $J = 7.8$ Hz, 2H), 6.82 (m, 1H), 6.74 (dd, $J = 2.4$, 1.4 Hz, 1H), 6.69 (m, 1H), 3.86 (s, 3H), 3.68 (dq, $J = 7.0$, 1.4 Hz, 1H), 2.68 (m, 2H), 1.50 (d, $J = 7.0$ Hz, 3H), 1.17 (d, $J = 6.9$ Hz, 6H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 200.6, 159.7, 146.5, 142.8, 138.8, 138.7, 127.9, 122.5, 121.9, 114.0, 112.3, 55.2, 52.8, 30.2, 24.3, 24.2, 24.12, 24.08, 14.4; IR (neat, KBr, $cm^{-1}$) 3059, 2961, 2868, 2719, 1726, 1587, 1454, 1202, 1053, 760; HRMS (FAB, $M^+$) *m/z* 324.2085 (calculated for $C_{22}H_{28}O_2$, 324.2089).

**General Procedure for the Ohira−Bestmann Homologation: 3-(3-Methoxy-5-(2,6-dimethylphenyl)phenyl)butyne (9c).** To a 0 °C solution of aldehyde **8c** (0.131 g, 0.488 mmol) in MeOH (2 mL) was added the Ohira−Bestmann reagent (0.143 g, 0.744 mmol)

dissolved in MeOH (1 mL) followed by powdered, anhydrous $K_2CO_3$ (0.141 g, 1.02 mmol). The mixture was stirred at 0 °C until the starting material had been consumed by TLC (1 h). The mixture was diluted with water (20 mL), and the aqueous phase was extracted with ether (3 × 15 mL). The combined extracts were washed with brine (20 mL), dried over sodium sulfate, and concentrated to afford the crude product that was purified by flash chromatography ($SiO_2$ 7 g, 2% EtOAc/hexanes) to afford biphenylacetylene **9c** as a colorless oil (0.117 g, 91%): TLC $R_f = 0.55$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.21 (m, 1H), 7.14 (m, 2H), 7.00 (m, 1H), 6.82 (m, 1H), 6.63 (m, 1H), 3.86 (s, 3H), 3.81 (dq, $J = 7.1$, 2.5 Hz, 1H), 2.30 (d, $J = 2.5$ Hz, 1H), 2.11 (s, 6H), 1.57 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.8, 144.3, 142.5, 141.7, 135.9, 127.2, 127.0, 120.1, 112.6, 110.9, 86.9, 70.3, 55.2, 31.6, 24.3, 20.7; IR (neat, KBr, $cm^{-1}$) 3292, 2975, 1593, 1456, 1207, 1045, 771; HRMS (FAB, $M^+$) *m/z* 264.1526 (calculated for $C_{19}H_{20}O$, 264.1514).

**3-(3-Methoxy-5-phenylphenyl)butyne (9a).** According to the general Ohira homologation procedure, aldehyde **8a** (0.187 g, 0.78 mmol), Ohira−Bestmann reagent (0.224 g, 1.16 mmol), and $K_2CO_3$ (0.215 g, 1.55 mmol) were reacted in methanol (4 mL) for 1.25 h. Following the general reaction workup, flash chromatography ($SiO_2$ 8 g, 2% EtOAc/hexanes) afforded alkyne **9a** as a clear oil (0.220 g, 64%): TLC $R_f = 0.44$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.62 (m, 2H), 7.47 (m, 2H), 7.38 (m, 1H), 7.24 (m, 1H), 7.04 (m, 1H), 6.99 (m, 1H), 3.90 (s, 3H), 3.84 (dq, $J = 7.1$, 2.5 Hz, 1H), 2.32 (d, $J = 2.5$ Hz, 1H), 1.59 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.2, 144.6, 143.0, 141.1, 128.7, 127.4, 127.2, 118.4, 111.6, 111.2, 86.9, 70.4, 55.3, 31.8, 24.2; IR (neat, KBr, $cm^{-1}$) 3290, 3034, 2976, 1595, 1421, 1213, 1049, 702; HRMS (FAB, $M^+$) *m/z* 236.1225 (calculated for $C_{17}H_{16}O$, 236.1201).

**3-(3-Methoxy-5-(2-methylphenyl)phenyl)butyne (9b).** According to the general Ohira homologation procedure, aldehyde **8b** (0.175 g, 0.688 mmol), Ohira−Bestmann reagent (0.202 g, 1.05 mmol), and $K_2CO_3$ (0.192 g, 1.39 mmol) were reacted in methanol (4 mL) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 8 g, 2% EtOAc/hexanes) afforded the biphenylacetylene **9b** as a clear oil (0.172 g, 99%): TLC $R_f = 0.44$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.29 (m, 4H), 7.05 (m, 2H), 6.85 (m, 1H), 3.91 (s, 3H), 3.87 (dq, $J = 7.1$, 2.5 Hz, 1H), 2.39 (s, 3H), 2.35 (d, $J = 2.5$ Hz, 1H), 1.64 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.5, 143.8, 143.4, 141.7, 135.2, 130.3, 129.6, 127.3, 125.7, 120.3, 113.0, 111.1, 86.8, 70.3, 55.2, 31.6, 24.2, 20.4; IR (neat, KBr, $cm^{-1}$) 3290, 2976, 1593, 1454, 1211, 710; HRMS (FAB, $M^+$) *m/z* 250.1369 (calculated for $C_{18}H_{18}O$, 250.1358).

**3-(3-Methoxy-5-(2,6-diisopropylphenyl)phenyl)butyne (9d).** According to the general Ohira homologation procedure, aldehyde **8d** (0.272 g, 0.838 mmol), Ohira−Bestmann reagent (0.251 g, 1.31 mmol), and $K_2CO_3$ (0.236 g, 1.71 mmol) were reacted in methanol (3.5 mL) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 15 g, 1% EtOAc/hexanes) afforded biphenylacetylene **9d** as a clear oil (0.214 g, 80%): TLC $R_f = 0.39$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36 (m, 1H), 7.23 (d, $J = 7.2$ Hz, 2H), 6.99 (m, 1H), 6.82 (m, 1H), 6.63 (dd, $J = 2.4$, 1.3 Hz, 1H), 3.84 (s, 3H), 3.79 (dq, $J = 7.1$, 2.4 Hz, 1H), 2.66 (m, 2H), 2.27 (d, $J = 2.4$ Hz, 1H), 1.54 (d, $J = 7.1$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 6H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 159.4, 146.71, 146.66, 143.8, 142.1, 139.3, 127.8, 120.8, 113.2, 110.8, 86.9, 70.2, 55.2, 31.6, 30.2, 24.34, 24.29, 24.2, 24.1; IR (neat, KBr, $cm^{-1}$) 3308, 3059, 2961, 2835, 2245, 1587, 1454, 1202, 1055, 739; HRMS (FAB, $M^+$) *m/z* 320.2140 (calculated for $C_{23}H_{28}O$, 320.2140).

**General Procedure for the Sonogashira Coupling: 2,4-Diamino-5-[3-(3-methoxy-5-(2,6-dimethylphenyl)phenyl)but-1-ynyl]-6-methylpyrimidine (10c).** To an oven-dried 8 mL screw cap vial was added iodopyrimidine **11** (0.074 g, 0.296 mmol), CuI (0.009 g, 0.047 mmol, ~15%), and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.026 mmol, ~8%). Degassed (argon purge) anhydrous DMF (0.5 mL) was added followed by alkyne **9c** (0.117 g, 0.442 mmol) as a solution in DMF (0.5 mL). Degassed (argon purge) anhydrous triethylamine was added (1 mL), and the mixture was degassed once using the freeze/pump/thaw method. The vial was sealed under argon and heated at 50 °C for 3 h. After the mixture was cooled, the orange solution was diluted with EtOAc (20 mL) and washed twice with a water/saturated $NaHCO_3$ solution (1:2, 20 mL) and brine (20 mL). The organic phase was dried over sodium sulfate and concentrated to afford the crude product that was purified by flash chromatography ($SiO_2$ 8 g, 2% MeOH/$CHCl_3$) to afford coupled pyrimidine **10c** as a pale solid (0.107 g, 94%). An analytical sample was generated by crystallization from cyclohexane. TLC $R_f = 0.27$ (EtOAc); mp 145−147 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.16 (m, 1H), 7.10 (m, 2H), 6.97 (m, 1H), 6.80 (m, 1H), 6.59 (dd, $J = 2.4$, 1.4 Hz, 1H), 5.14 (bs, 2H), 4.88 (bs, 2H), 4.04 (q, $J = 7.1$ Hz, 1H), 3.82 (s, 3H), 2.35 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.60 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.1, 160.4, 159.9, 145.0, 142.8, 141.6, 135.89, 135.87, 127.3, 127.1, 120.0, 112.6, 110.9, 101.9, 91.5, 75.5, 55.3, 33.0, 24.6, 22.8, 20.74, 20.72; HRMS (FAB, $M^+$) *m/z* 386.2110 (calculated for $C_{24}H_{26}N_4O$, 386.2107); HPLC (a) $t_R = 5.19$ min, 98.9%, (b) $t_R = 4.94$ min, 98.2%.

**2,4-Diamino-5-[3-(3-methoxy-5-phenylphenyl)but-1-ynyl]-6-methylpyrimidine (10a).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.080 g, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (0.016 g, 0.023 mmol, 7%), CuI (0.0010 g, 0.026 mmol, 16%), and alkyne **9a** (0.131 g, 0.554 mmol) were reacted in DMF/$Et_3N$ (1.25 mL each) at 50 °C for 4 h. Following the general workup procedure, flash chromatography ($SiO_2$ 17 g, EtOAc) afforded coupled pyrimidine **10a** as a white foam (0.095 g, 82%): TLC $R_f = 0.22$ (EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.43 (m, 2H), 7.35 (m, 1H), 7.24 (m, 1H), 7.02 (m, 1H), 6.99 (m, 1H), 5.19 (bs, 2H), 4.95 (bs, 2H), 4.08 (q, $J = 7.1$ Hz, 1H), 3.87 (s, 3H), 2.39 (s, 3H), 1.63 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.1, 160.4, 160.2, 145.3, 143.1, 141.0, 128.8, 127.5, 127.2, 118.3, 111.5, 111.1, 101.7, 91.4, 75.7, 55.4, 33.1, 24.7, 22.8; HRMS (FAB, $M^+$) *m/z* 358.1805 (calculated for $C_{22}H_{22}N_4O$, 358.1794); HPLC (a) $t_R = 6.94$ min, 100%, (b) $t_R = 6.99$ min, 100%.

**2,4-Diamino-5-[3-(3-methoxy-5-(2-methylphenyl)phenyl)but-1-ynyl]-6-methylpyrimidine (10b).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.091 g, 0.364 mmol), $Pd(PPh_3)_2Cl_2$ (0.022 g, 0.031 mmol), CuI (0.011 g, 0.058 mmol), and alkyne **9b** (0.138 g, 0.551 mmol) were reacted in DMF/$Et_3N$ (1.25 mL each) at 50 °C for 3 h. Following the general workup procedure, flash chromatography ($SiO_2$ 8 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **10b** as a pale solid (0.118 g, 86%). An analytical sample was generated by crystallization from ether/hexanes. TLC $R_f = 0.24$ (EtOAc); mp 121.0−123.0 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28−7.23 (m, 4H), 6.98 (m, 1H), 6.96 (m, 1H), 6.76 (dd, $J = 2.3$, 1.5 Hz, 1H), 5.12 (bs, 2H), 4.83 (bs, 2H), 4.05 (q, $J = 7.1$ Hz, 1H), 3.84 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H), 1.62 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.0, 160.4, 159.5, 144.5, 143.6, 141.6, 135.2, 130.3, 129.5, 127.4, 125.7, 120.3, 113.0, 111.1, 101.8, 91.4, 75.5, 55.3, 33.0, 24.7, 22.8, 20.5; HRMS (FAB, $M^+$) *m/z* 372.1956 (calculated for $C_{23}H_{24}N_4O$, 372.1950); HPLC (a) $t_R = 7.70$ min, 99.6%, (b) $t_R = 7.59$ min, 99.4%.

**2,4-Diamino-5-[3-(3-methoxy-5-(2,6-diisopropylphenyl)phenyl)-but-1-ynyl]-6-methylpyrimidine (10d).** According to the general Sonagashira coupling procedure iodopyrimidine **11** (0.110 g, 0.44 mmol), $Pd(PPh_3)_2Cl_2$ (0.026 g, 0.037 mmol), CuI (0.011 g, 0.058 mmol), and alkyne **9d** (0.210 g, 0.655 mmol) were reacted in DMF/$Et_3N$ (1.25 mL each) at 50 °C for 3.5 h. Following the general workup procedure flash chromatography ($SiO_2$ 15 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **10d** as a pale solid (0.131 g, 67%). An analytical sample was generated by crystallization from 5% EtOAc/hexanes. TLC $R_f = 0.28$ (EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (m, 1H), 7.20 (m, 2H), 6.99 (m, 1H), 6.82 (m, 1H), 6.62 (dd, $J = 2.5$, 1.3 Hz, 1H), 5.16 (bs, 2H), 4.94 (bs, 2H), 4.04 (q, $J = 7.2$ Hz, 1H), 3.82 (s, 3H), 2.64 (m, 2H), 2.35 (s, 3H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.13−1.04 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.0, 160.4, 159.4, 146.63, 146.61, 144.4, 142.3, 139.2, 127.9, 122.53, 122.51, 120.7, 113.2, 110.9, 101.7, 91.4, 75.5,

55.3, 33.0, 30.23, 30.21, 24.7, 24.31, 24.30, 24.22, 24.16, 22.8; HRMS (FAB, $M^+$) *m/z* 442.2730 (calculated for $C_{28}H_{34}N_4O$, 442.2733); HPLC (a) $t_R$ = 8.79 min, 98.7%, (b) $t_R$ = 7.42 min, 98.4%.

**1-(4-Bromo-3-methoxyphenyl)ethanone (13).** To a 0 °C suspension of benzoic acid **12** (2.00 g, 8.66 mmol) in dry $CH_2Cl_2$ (42 mL) and dry benzene (17 mL) with 8 drops (from 18G needle) of anhydrous DMF was added oxalyl chloride (0.84 mL, 9.62 mmol) dropwise. Evolution of gas was observed during the addition, and suspended solids began to go into solution. The mixture was warmed to ambient temperature and stirred until all of solids had gone into solution (2.5 h). The volatile components were evaporated, and the crude white solid was dried under high vacuum for 10 h and then used directly in the next step. To a −78 °C suspension of powdered CuI (6.59 g, 34.6 mmol) in anhydrous THF (70 mL) was added MeLi (3 M in DME, 11.6 mL, 34.8 mmol) dropwise, quickly. The mixture was stirred for 5 min at −78 °C and then for 15 min at 0 °C. The now clear solution containing yellow solids was cooled to −78 °C, and a cooled (−78 °C) solution of the crude acid chloride in THF (30 mL) was added dropwise via cannula. The mixture was stirred for 40 min at −78 °C. Then 3 mL of methanol was added and the mixture warmed to ambient temperature. The reaction contents were poured into saturated $NH_4Cl$ (200 mL), diluted with ether (50 mL), and stirred vigorously for 1 h. The organic phase was separated, and the aqueous phase was extracted with ether (4 × 30 mL). The combined extracts were washed with saturated $NH_4Cl$, water, and brine (75 mL each), dried over sodium sulfate, and concentrated. The crude oil was purified by flash chromatography (60 g $SiO_2$, 5% EtOAc/hexanes) to provide ketone **13** as an amber oil that solidified very slowly in the freezer (1.78 g, 90%): TLC $R_f$ = 0.20 (5% EtOAc/hexanes); mp 31.5−32.0 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 8.1 Hz, 1H), 7.50 (d, $J$ = 1.9 Hz, 1H), 7.40 (dd, $J$ = 8.1, 1.9 Hz, 1H), 3.96 (s, 3H), 2.60 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 196.9, 156.2, 137.5, 133.3, 122.1, 117.9, 110.4, 56.3, 26.5; IR (neat, KBr, $cm^{-1}$) 3072, 2941, 1682, 1583, 1402, 1283, 1024, 704; HRMS (FAB, $MH^+$) *m/z* 228.9848 (calculated for $C_9H_{10}BrO_2$, 228.9864).

**1-(3-Methoxy-4-phenyl)phenylethanone (14a).** According to the general Suzuki coupling procedure, ketone **13** (0.470 g, 2.05 mmol) was reacted with phenylboronic acid **6a** (0.502 g, 4.12 mmol), $Cs_2CO_3$ (2.01 g, 6.17 mmol), and $Pd(PPh_3)_2Cl_2$ (0.081 g, 0.12 mmol, 6% Pd) in 4 mL of dioxane for 22 h. Following the general reaction workup, flash chromatography ($SiO_2$ 21 g, 2−5% EtOAc/hexanes) afforded biphenyl ketone **14a** as a white solid (0.457 g, 98%): TLC $R_f$ = 0.43 (15% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65−7.56 (m, 4H), 7.49−7.35 (m, 4H), 3.88 (s, 3H), 2.65 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.5, 156.5, 137.23, 137.17, 135.5, 130.6, 129.3, 128.0, 127.5 121.6, 109.8, 55.5, 26.5; IR (neat, KBr, $cm^{-1}$) 3074, 3003, 1675, 1599, 1398, 1223, 1033, 873; HRMS (FAB, $MH^+$) *m/z* 227.1073 (calculated for $C_{15}H_{15}O_2$, 227.1072).

**1-(3-Methoxy-4-(2-methylphenyl)phenyl)ethanone (14b).** According to the general Suzuki coupling procedure, ketone **13** (0.491 g, 2.14 mmol) was reacted with 2-methylphenylboronic acid **6b** (0.582 g, 4.28 mmol), $Cs_2CO_3$ (2.09 g, 6.42 mmol), and $Pd(PPh_3)_2Cl_2$ (0.080 g, 0.11 mmol, 5% Pd) in 4.3 mL of dioxane for 21 h. Following the general reaction workup, flash chromatography ($SiO_2$ 16 g, 2−5% EtOAc/hexanes) afforded biphenyl ketone **14b** as a clear oil (0.490 g, 95%): TLC $R_f$ = 0.44 (15% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.67 (m, 2H), 7.36−7.26 (m, 4H), 7.23 (m, 1H), 3.87 (s, 3H), 2.70 (s, 3H), 2.20 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.6, 156.8, 137.4, 136.3, 136.1, 130.9, 129.6, 129.4, 127.6, 125.4, 121.3, 109.2, 55.4, 26.4, 19.7 (one aromatic carbon unresolved); IR (neat, KBr, $cm^{-1}$) 3063, 2961, 1680, 1288, 1218, 1034; HRMS (FAB, $M^+$) *m/z* 240.1148 (calculated for $C_{16}H_{16}O_2$, 240.1150).

**1-(3-Methoxy-4-(2,6-dimethylphenyl)phenyl)ethanone (14c).** According to the general Suzuki coupling procedure, ketone **13** (0.312 g, 1.36 mmol) was reacted with 2,6-dimethylphenylboronic acid **6c** (0.410 g, 2.73 mmol), $Cs_2CO_3$ (1.33 g, 4.08 mmol), and $Pd(PPh_3)_2Cl_2$ (0.080 g, 0.11 mmol, 5% Pd) in 2.8 mL of dioxane for 23 h. Following the general reaction workup, flash chromatography ($SiO_2$ 11 g, 5% EtOAc/hexanes) afforded biphenyl ketone **14c** as a very viscous oil that slowly formed a solid (0.325 g, 93%): TLC $R_f$ = 0.45 (15% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.66 (m, 2H), 7.25−7.12 (m, 4H), 3.83 (s, 3H), 2.68 (s, 3H), 2.04 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 156.8, 137.5, 137.1, 136.0, 135.1, 130.7, 127.4, 127.1, 121.6, 109.5, 55.5, 26.5, 20.2; IR (neat, KBr, $cm^{-1}$); HRMS (FAB, $MH^+$) *m/z* 255.1396 (calculated for $C_{17}H_{19}O_2$, 255.1385).

**1-(4-(2,6-Diisopropylphenyl)-3-methoxyphenyl)ethanone (14d).** According to the general Suzuki coupling procedure, ketone **13** (0.251 g, 1.09 mmol) was reacted with boronic acid **6d** (0.451 g, 2.19 mmol), $Cs_2CO_3$ (1.07 g, 3.28 mmol), and $Pd(PPh_3)_2Cl_2$ (0.040 g, 0.056 mmol, 5% Pd) in 2 mL of dioxane for 17.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 13 g, 2% EtOAc/hexanes) afforded biphenyl ketone **14d** as a viscous, clear oil (0.328 g, 96%): TLC $R_f$ = 0.19 (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.65 (m, 2H), 7.41 (t, $J$ = 7.7 Hz, 1H), 7.27 (d, $J$ = 7.7 Hz, 2H), 7.21 (m, 1H), 3.82 (s, 3H), 2.69 (s, 3H), 2.53 (sep, $J$ = 6.9 Hz, 2H), 1.12 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 197.7, 157.5, 146.6, 137.5, 135.0, 134.5, 131.1, 128.2, 122.4, 121.2, 109.1, 55.3, 30.6, 26.5, 24.1, 23.7; IR (neat, KBr, $cm^{-1}$) 3063, 2962, 1684, 1603, 1081, 1034, 762; HRMS (FAB, $M^+$) *m/z* 310.1925 (calculated for $C_{21}H_{26}O_2$, 310.1933).

**2-(3-Methoxy-4-phenylphenyl)propanal (15a).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (1.20 g, 3.5 mmol), NaO$^t$Bu (0.433 g, 4.5 mmol), and biphenyl ketone **14a** (0.457 g, 2.0 mmol) gave, following filtration ($SiO_2$ 21 g, 1% EtOAc/hexanes), 0.504 g of a mixture (*E*/*Z* ≈ 1:1) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f$ = 0.43 (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.504 g) was reacted with concentrated HCl (0.5 mL) in THF (10 mL) for 1 h. Following the general reaction workup, flash chromatography ($SiO_2$ 22 g, 2−5% EtOAc/hexanes) afforded aldehyde **15a** as a clear oil (0.437 g, 90% from **14a**): TLC $R_f$ = 0.19 (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.76 (d, $J$ = 1.4 Hz, 1H), 7.56 (m, 2H), 7.45 (m, 2H), 7.36 (m, 2H), 6.93 (dd, $J$ = 7.7, 1.7 Hz, 1H), 6.83 (d, $J$ = 1.7 Hz, 1H), 3.84 (s, 3H), 3.70 (dq, $J$ = 7.0, 1.4 Hz, 1H), 1.53 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.8, 156.9, 138.2, 137.9, 131.3, 129.9, 129.4, 128.0, 127.0 120.6 111.1, 55.5, 53.0, 14.5; IR (neat, KBr, $cm^{-1}$) 3028, 2974, 2719, 1728, 1485, 1273, 1034; HRMS (FAB, $M^+$) *m/z* 240.1166 (calculated for $C_{16}H_{16}O_2$, 240.1150).

**2-(3-Methoxy-4-(2-methylphenyl)phenyl)propanal (15b).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (1.23 g, 3.6 mmol), NaO$^t$Bu (0.440 g, 4.6 mmol), and biphenyl ketone **14b** (0.490 g, 2.04 mmol) gave, following filtration ($SiO_2$ 28 g, 1% EtOAc/hexanes), 0.520 g of a mixture (*E*/*Z* ≈ 60:40) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f$ = 0.38 (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.520 g) was reacted with concentrated HCl (0.5 mL) in THF (10 mL) for 1 h. Following the general reaction workup, flash chromatography ($SiO_2$ 23 g, 2−5% EtOAc/hexanes) afforded aldehyde **15b** as a clear oil (0.425 g, 82% from **14b**): TLC $R_f$ = 0.19 (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.77 (d, $J$ = 1.4 Hz, 1H), 7.30−7.15 (m, 5H), 6.89 (dd, $J$ = 7.6, 1.6 Hz, 1H), 6.79 (d, $J$ = 1.6 Hz, 1H), 3.78 (s, 3H), 3.71 (dd, $J$ = 7.0, 1.4 Hz, 1H), 2.16 (s, 3H), 1.52 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.0, 157.1, 138.1, 138.0, 136.8, 131.5, 130.1, 130.0, 129.6, 127.4, 125.4, 120.2, 110.6, 55.4, 53.1, 19.9, 14.5; IR (neat, KBr, $cm^{-1}$) 3016, 2974, 2719, 1728, 1610, 1456, 1269, 1034; HRMS (FAB, $M^+$) *m/z* 254.1326 (calculated for $C_{17}H_{18}O_2$, 254.1307).

**2-(3-Methoxy-4-(2,6-dimethylphenyl)phenyl)propanal (15c).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (0.78 g, 2.3 mmol), NaO$^t$Bu (0.287 g, 3.0 mmol), and biphenyl ketone **14c** (0.304 g, 1.2 mmol) gave, following filtration ($SiO_2$ 12 g, 2% EtOAc/hexanes), 0.356 g of a

mixture (*E*/*Z* ≈ 65:35) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f = 0.37$ (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.356 g) was reacted with concentrated HCl (0.5 mL) in THF (7 mL) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 15 g, 2−5% EtOAc/hexanes) afforded aldehyde **15c** as a clear oil (0.294 g, 92% from **14c**): TLC $R_f =$ 0.19 (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.80 (d, $J = 1.5$ Hz, 1H), 7.22 (m, 1H), 7.16 (m, 2H), 7.09 (d, $J = 7.6$ Hz, 1H), 6.94 (dd, $J = 7.6$, 1.5 Hz, 1H), 6.84 (d, $J = 1.5$ Hz, 1H), 3.78 (s, 3H), 3.74 (dq, $J = 7.0$, 1.5 Hz, 1H), 2.07 (s, 6H), 1.56 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 201.0, 156.8, 137.7, 137.5, 136.5, 131.1, 128.6, 127.1, 126.9, 120.3, 110.6, 55.3, 53.0, 20.4, 14.4; IR (neat, KBr, cm$^{-1}$) 2974, 2719, 1731, 1456, 1269, 1040, 773; HRMS (FAB, $M^+$) *m*/*z* 268.1475 (calculated for $C_{18}H_{20}O_2$, 268.1463).

**2-(3-Methoxy-4-(2,6-diisopropylphenyl)phenyl)propanal (15d).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (0.622 g, 1.8 mmol), NaO$^t$Bu (0.225 g, 2.3 mmol), and biphenyl ketone **14d** (0.326 g, 1.05 mmol) gave, following filtration ($SiO_2$ 20 g, 1% EtOAc/hexanes), 0.364 g of crude material that was immediately hydrolyzed in the subsequent step: TLC $R_f = 0.44$ (5% EtOAc/hexanes).

According to the general hydrolysis procedure, the crude enol ether (0.334 g) was reacted with concentrated HCl (0.5 mL) in THF (8 mL) for 2 h. Following the general reaction workup, flash chromatography ($SiO_2$ 19 g, 2−5% EtOAc/hexanes) afforded aldehyde **15d** as a viscous oil (0.272 g, 76% from **14d**): TLC $R_f =$ 0.24 (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.80 (d, $J = 1.6$ Hz, 1H), 7.38 (m, 1H), 7.24 (d, $J = 7.4$ Hz, 2H), 7.08 (d, $J = 7.6$ Hz, 1H), 6.90 (dd, $J = 7.6$, 1.5 Hz, 1H), 6.80 (d, $J =$ 1.5 Hz, 1H), 3.74 (s, 3H), 3.73 (dq, $J = 7.1$, 1.6 Hz, 1H), 2.56 (sep, $J = 6.9$ Hz, 2H), 1.56 (d, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 6.9$ Hz, 6H), 1.10 (d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 201.1, 157.6, 147.1 137.7, 135.1, 131.6, 128.4, 127.9, 122.4, 120.0, 110.2, 55.1, 53.0, 30.5, 24.2, 23.7, 14.4; IR (neat, KBr, cm$^{-1}$) 3061, 2959, 2868, 2719, 1725, 1568, 1269, 1038, 764; HRMS (FAB, $M^+$) *m*/*z* 324.2103 (calculated for $C_{22}H_{28}O_2$, 324.2089).

**3-(3-Methoxy-4-phenylphenyl)butyne (16a).** According to the general Ohira homologation procedure, aldehyde **15a** (0.437 g, 1.82 mmol), Ohira−Bestmann reagent (0.523 g, 2.72 mmol), and $K_2CO_3$ (0.505 g, 3.05 mmol) were reacted in methanol (25 mL, too much solvent used in this example) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 20 g, 2% EtOAc/hexanes) afforded biphenylacetylene **16a** as a clear oil (0.220 g, 51%, low yield likely because of high dilution): TLC $R_f = 0.39$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.46 (m, 2H), 7.36 (m, 2H), 7.10 (m, 2H), 3.88 (s, 3H), 3.86 (dq, $J = 7.1$, 2.5 Hz, 1H), 2.35 (d, $J = 2.5$ Hz, 1H), 1.62 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.5, 143.3, 138.3, 130.9, 129.5, 129.2, 127.9, 126.8, 119.1, 109.9, 87.0, 70.3, 55.5, 31.6, 24.1; IR (neat, KBr, cm$^{-1}$) 3288, 3028, 2975, 1614, 1409, 1274, 1040, 700; HRMS (FAB, $M^+$) *m*/*z* 236.1219 (calculated for $C_{17}H_{16}O$, 236.1201).

**3-(3-Methoxy-4-(2-methylphenyl)phenyl)butyne (16b).** According to the general Ohira homologation procedure, aldehyde **15b** (0.425 g, 1.67 mmol), Ohira−Bestmann reagent (0.483 g, 2.51 mmol), and $K_2CO_3$ (0.465 g, 3.36 mmol) were reacted in methanol (24 mL, too much solvent used in this example) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 22 g, 2% EtOAc/hexanes) afforded the biphenylacetylene **16b** as a clear oil (0.290 g, 70%): TLC $R_f = 0.39$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36−7.24 (m, 4H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.11 (m, 2H), 3.92 (dq, $J = 7.1$, 2.5 Hz, 1H), 3.86 (s, 3H), 2.39 (d, $J = 2.5$ Hz, 1H), 2.24 (s, 3H), 1.67 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.6, 143.2, 138.4, 136.8, 131.0, 130.1, 129.5, 129.3, 127.2, 125.4, 118.7, 109.3, 87.1, 70.3, 55.3, 31.7, 24.2, 19.9; IR (neat, KBr, cm$^{-1}$) 3288, 3016, 2975, 2247, 1612, 1412, 1238, 1039, 729; HRMS (FAB, $M^+$) *m*/*z* 250.1346 (calculated for $C_{18}H_{18}O$, 250.1358).

**3-(3-Methoxy-4-(2,6-dimethylphenyl)phenyl)butyne (16c).** According to the general Ohira homologation procedure, aldehyde **15c** (0.284 g, 1.06 mmol), Ohira−Bestmann reagent (0.307 g, 1.60 mmol), and $K_2CO_3$ (0.293 g, 2.12 mmol) were reacted in methanol (15 mL, too much solvent used in this example) for 2 h. Following the general reaction workup, flash chromatography ($SiO_2$ 13 g, 2% EtOAc/hexanes) afforded biphenylacetylene **16c** as a white solid (0.210 g, 75%): TLC $R_f = 0.43$ (5% EtOAc/hexanes); mp 46.3−47.6 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 156.5, 142.9, 137.9, 136.7, 130.6, 127.8, 126.99, 126.95, 118.9, 109.5, 87.1, 70.3, 55.3, 31.7, 24.3, 20.5; IR (neat, KBr, cm$^{-1}$) 3290, 3016, 2976, 2245, 1610, 1464, 1244, 1039, 733; HRMS (FAB, $M^+$) *m*/*z* 264.1515 (calculated for $C_{19}H_{20}O$, 264.1514).

**3-(3-Methoxy-4-(2,6-diisopropylphenyl)phenyl)butyne (16d).** According to the general Ohira homologation procedure, aldehyde **15d** (0.270 g, 0.832 mmol), Ohira−Bestmann reagent (0.248 g, 1.29 mmol), and $K_2CO_3$ (0.231 g, 1.67 mmol) were reacted in methanol (3.5 mL) for 1.5 h. Following the general reaction workup, flash chromatography ($SiO_2$ 15 g, 1% EtOAc/hexanes) afforded biphenylacetylene **16d** as a clear oil (0.181 g, 68%): TLC $R_f = 0.39$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38 (dd, $J =$ 8.3, 7.2 Hz, 1H), 7.24 (d, $J = 7.5$ Hz, 2H), 7.06−6.99 (m, 3H), 3.89 (dq, $J = 7.2$, 2.5 Hz, 1H), 3.76 (s, 3H), 2.60 (m, 2H), 2.53 (d, $J = 2.5$ Hz, 1H), 1.64 (d, $J = 7.2$ Hz, 3H), 1.14−1.07 (m, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.2, 147.3, 142.8, 135.5, 131.1, 127.8, 127.4, 122.4, 118.5, 109.1, 87.2, 70.3, 55.1, 31.7, 30.4, 24.3, 23.8; IR (neat, KBr, cm$^{-1}$); HRMS (FAB, $M^+$) *m*/*z* 320.2149 (calculated for $C_{23}H_{28}O$, 320.2140).

**2,4-Diamino-5-[3-(3-methoxy-4-phenylphenyl)but-1-ynyl]-6-methylpyrimidine (17a).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.084 g, 0.336 mmol), $Pd(PPh_3)_2Cl_2$ (0.023 g, 0.033 mmol), CuI (0.012 g, 0.063 mmol), and alkyne **16a** (0.117 g, 0.495 mmol) were reacted in DMF/$Et_3N$ (1 mL each) at 50 °C for 3 h. Following the general workup procedure flash chromatography ($SiO_2$ 10 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **17a** as a pale solid (0.103 g, 85%). An analytical sample was generated by crystallization from ether/hexanes. TLC $R_f = 0.23$ (EtOAc); mp 163.2−165.2 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.53 (m, 2H), 7.40 (m, 2H), 7.34−7.29 (m, 2H), 7.10−7.07 (m, 2H), 5.17 (bs, 2H), 4.90 (bs, 2H), 4.09 (q, $J =$ 7.1 Hz, 1H), 3.83 (s, 3H), 2.41 (s, 3H), 1.65 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.1, 160.5, 156.6, 144.1, 138.2, 131.0, 129.5, 129.3, 128.0, 126.9, 119.1, 109.9, 101.8, 91.4, 75.7, 55.6, 33.0, 24.7, 22.9; HRMS (FAB, $M^+$) *m*/*z* 358.1815 (calculated for $C_{22}H_{22}N_4O$, 358.1794); HPLC (a) $t_R = 5.62$ min, 97.7%, (b) $t_R = 6.55$ min, 96.9%.

**2,4-Diamino-5-[3-(3-methoxy-4-(2-methylphenyl)phenyl)but-1-ynyl]-6-methylpyrimidine (17b).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.083 g, 0.331 mmol), $Pd(PPh_3)_2Cl_2$ (0.023 g, 0.033 mmol), CuI (0.012 g, 0.063 mmol), and alkyne **16b** (0.125 g, 0.498 mmol) were reacted in DMF/$Et_3N$ (1 mL each) at 50 °C for 2.5 h. Following the general workup procedure flash chromatography ($SiO_2$ 10 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **17b** as a pale solid (0.103 g, 97%). An analytical sample was generated by crystallization from ether/hexanes. TLC $R_f = 0.25$ (EtOAc); mp 177.2−180.1 °C, with dec; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.26−7.20 (m, 3H), 7.18 (m, 1H), 7.12 (m, 1H), 7.07−7.04 (m, 2H), 5.15 (bs, 2H), 4.86 (bs, 2H), 4.10 (q, $J = 7.1$ Hz, 1H), 3.77 (s, 3H), 2.41 (s, 3H), 2.15 (s, 3H), 1.66 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.1, 160.4, 156.8, 143.9, 138.3, 136.9, 131.2, 130.1, 129.6, 129.4, 127.3, 125.4, 118.7, 109.3, 101.9, 91.5, 75.7, 55.4, 33.1, 24.8, 22.9, 20.0; HRMS (FAB, $M^+$) *m*/*z* 372.1933 (calculated for $C_{23}H_{24}N_4O$, 372.1950); HPLC (a) $t_R = 6.33$ min, 98.5%, (b) $t_R =$ 7.16 min, 97.3%.

**2,4-Diamino-5-[3-(3-methoxy-4-(2,6-dimethylphenyl)phenyl)but-1-ynyl]-6-methylpyrimidine (17c).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.080 g, 0.319 mmol), $Pd(PPh_3)_2Cl_2$ (0.022 g, 0.031 mmol), CuI (0.011 g, 0.058 mmol), and alkyne **16c** (0.125 g, 0.473 mmol) were reacted in DMF/$Et_3N$ (1 mL each) at 50 °C for 3.5 h. Following the general workup

procedure flash chromatography ($SiO_2$ 9 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **17c** as a pale solid (0.121 g, 98%). An analytical sample was generated by crystallization from ether/hexanes. TLC $R_f = 0.26$ (EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.16 (dd, $J = 8.4$, 6.5 Hz, 1H), 7.10 (bd, $J = 7.5$ Hz, 2H), 7.06 (m, 2H), 7.00 (d, $J = 8.1$ Hz, 1H), 5.20 (bs, 2H), 4.94 (bs, 2H), 4.11 (q, $J = 7.1$ Hz, 1H), 3.74 (s, 3H), 2.41 (s, 3H), 2.02 (s, 6H), 1.67 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.5, 164.2, 160.4, 156.7, 143.6, 137.9, 136.70, 136.67, 130.8, 128.0, 127.1, 127.0, 118.9, 109.5, 102.0, 91.5, 75.7. 55.5, 33.0, 24.7, 20.5; HRMS (FAB, $M^+$) *m/z* 386.2092 (calculated for $C_{24}H_{26}N_4O$, 386.2107); HPLC (a) $t_R = 4.42$ min, 98.8%, (b) $t_R = 4.70$ min, 98.7%.

**2,4-Diamino-5-[3-(3-methoxy-4-(2,6-diisopropylphenyl)phenyl)-but-1-ynyl]-6-methylpyrimidine (17d).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.086 g, 0.34 mmol), $Pd(PPh_3)_2Cl_2$ (0.023 g, 0.033 mmol), CuI (0.008 g, 0.042 mmol), and alkyne **16d** (0.166 g, 0.518 mmol) were reacted in DMF/$Et_3N$ (1 mL each) at 50 °C for 3 h. Following the general workup procedure flash chromatography ($SiO_2$ 15 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine **17d** as a pale solid (0.131 g, 53%). An analytical sample was generated by crystallization from cyclohexane. TLC $R_f = 0.29$ (EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35 (t, $J = 7.7$ Hz, 1H), 7.21 (d, $J = 7.7$ Hz, 2H), 7.04 (m, 2H), 7.00 (d, $J = 8.0$ Hz, 1H), 5.13 (bs, 2H), 4.81 (bs, 2H), 4.12 (q, $J = 7.1$ Hz, 1H), 3.72 (s, 3H), 2.56 (sep, $J = 6.9$ Hz, 2H), 2.41 (s, 3H), 1.69 (d, $J = 7.1$ Hz, 3H), 1.10−1.04 (m, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.6, 164.1, 160.4, 157.3, 147.3, 147.2, 143.5, 135.4, 131.3, 127.8, 127.5, 122.4, 118.4, 109.0, 102.1, 91.5, 75.8, 55.1, 33.0, 30.5, 24.6, 24.3, 23.8, 22.8; HRMS (FAB, $M^+$) *m/z* 442.2709 (calculated for $C_{28}H_{34}N_4O$, 442.2733); HPLC (a) $t_R = 7.58$ min, 99.0%, (b) $t_R = 7.06$ min, 100%.

**3-Bromo-5-methoxybenzaldehyde.** To a stirring −78 °C solution of *n*-BuLi (in hexanes, 1.7 M, 11.25 mL, 19.1 mmol) in dry ether (24 mL) under argon was added a solution of dibromoanisole **4** (5.08 g, 19.1 mmol) dissolved in ether (12 mL) dropwise via cannula. A white precipitate formed, and the mixture was stirred at −78 °C for 20 min. Dimethylformamide (1.6 mL, 20.6 mmol) was added dropwise generating a homogeneous solution that was stirred an additional 20 min at −78 °C. The reaction was quenched by the addition of 10% aqueous HCl (30 mL), and the mixture was allowed to warm to ambient temperature. The organic phase was separated, and the aqueous layer was extracted once with ether (40 mL). The combined extracts were washed with saturated $NaHCO_3$ and brine (30 mL each), dried over sodium sulfate, and concentrated to give 3-bromo-5-methoxybenzaldehyde as an amber solid with sufficient purity for subsequent transformations (4.04 g, 98%). Flash chromatography of 0.5 g of material ($SiO_2$ 20 g, 5% EtOAc/hexanes) provided an analytical sample: TLC $R_f = 0.19$ (5% EtOAc/hexanes); mp 39.7 − 40.4 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.88 (s, 1H), 7.54 (m, 1H), 7.29 (m, 1H), 7.28 (m, 1H), 3.85 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 190.4, 160.7, 138.5, 125.5, 123.6, 123.4, 112.1, 55.7; IR (neat, KBr, $cm^{-1}$).

**3-Methoxy-5-phenylbenzaldehyde (18).** According to the general Suzuki coupling procedure, 3-bromo-5-methoxybenzaldehyde (4.04 g, 18.8 mmol) was reacted with phenylboronic acid (4.58 g, 37.5 mmol), $Cs_2CO_3$ (18.0 g, 55.2 mmol), and $Pd(PPh_3)_2Cl_2$ (0.263 g, 0.374 mmol, 2% Pd) in 38 mL of dioxane for 3 h. Following the general reaction workup, flash chromatography ($SiO_2$ 140 g, 2 − 5% EtOAc/hexanes) afforded aldehyde **18** as a viscous oil (3.29 g, 82%): TLC $R_f = 0.42$ (15% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.05 (s, 1H), 7.69 (m, 1H), 7.63 (m, 1H), 7.61 (m, 1H), 7.48 (m, 2H), 7.42−7.38 (m, 3H), 3.93 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 192.1, 160.6, 143.5, 139.6, 138.2, 129.0, 128.1, 127.1, 122.4, 120.1, 110.9, 55.7; IR (neat, KBr, $cm^{-1}$) 3063, 2939, 2734, 1699, 1593, 1332, 1217, 1049; HRMS (FAB, $M^+$) *m/z* 212.0826 (calculated for $C_{14}H_{12}O_2$, 212.0837).

**(3-Methoxy-5-phenyl)phenylacetic Acid (19).** According to the general Wittig reaction procedure, the reaction of phosphonium chloride (9.08 g, 26.5 mmol), NaO$^t$Bu (3.26 g, 33.9 mmol), and aldehyde **18** (3.20 g, 15.1 mmol) gave, following chromatography ($SiO_2$ 100 g, 1−5% EtOAc/hexanes), 3.88 g of a mixture (*E*/*Z* ≈ 1:1) of enol ethers that were immediately hydrolyzed in the subsequent step: TLC $R_f = 0.31$ (5% EtOAc/hexanes).

The enol ether mixture previously obtained was dissolved in THF (75 mL), and 2 N HCl was added (1 mL). The flask was fitted with a reflux condenser and the mixture heated to reflux. The reaction was monitored by TLC until the disappearance of starting material was observed (∼2 h). Extended reaction times increase the incidence of aldol products, so this should be avoided. The mixture was cooled, diluted with ethyl acetate (100 mL), and washed with $NaHCO_3$ (2 × 30 mL), water (30 mL), and brine (30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to provide the crude aldehyde (3.5 g) that was immediately used in the following oxidation. Purification of this aldehyde prior to oxidation resulted in a decrease in overall yield of carboxylic acid from arylaldehyde, presumably because of instability of the alkylaldehyde to chromatographic conditions.

To the crude aldehyde (3.5 g) in acetone (130 mL) at 0 °C was added freshly prepared Jones' reagent dropwise until the solution became a dark-red color. After the mixture was stirred for 5 min, isopropyl alcohol was added until a dark-green mixture formed. The mixture was concentrated on a rotovap and dried under a high vacuum for a short time (∼30 min). The dark-green crusty residue was suspended in NaOH (1 N, 200 mL) and transferred to a separatory funnel where it was washed with two portions of ether (75 mL each). The aqueous phase was acidified with concentrated HCl to pH ∼1 and extracted with $CH_2Cl_2$ (100 mL × 3). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated to provide carboxylic acid **19** as a white solid (2.63 g, 72% three steps): TLC $R_f = 0.08$ (50% EtOAc/hexanes); mp 140.4 − 141.6 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.7 (bs, 1H), 7.57 (m, 2H), 7.43 (m, 2H), 7.35 (m, 1H), 7.10 (m, 1H), 7.05 (m, 1H), 6.84 (m, 1H), 3.86 (s, 3H), 3.69 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 177.4, 160.1, 143.1, 140.7, 134.9, 128.7, 127.5, 127.2, 120.9, 113.8, 112.0, 55.4, 41.2; HRMS (FAB $M^+$) *m/z* 242.0943 (calculated for $C_{15}H_{14}O_3$, 242.0943).

**(*S*)-4-Isopropyl-3-(2-(3-methoxy-5-phenylphenyl)acetyl)oxazolidin-2-one (20).** To a solution of carboxylic acid **19** (1.24 g, 5.11 mmol) in dry THF (25 mL) was added $Et_3N$ (0.78 mL, 5.61 mmol). The solution was cooled to −78 °C, and pivolyl chloride (0.69 mL, 5.6 mmol) was added dropwise. A precipitate formed, and the mixture was stirred an additional 15 min at −78 °C and then at 0 °C for 1 h. In a separate flame-dried round-bottomed flask was added the Evans (*S*)-isopropyloxazoldinone (0.552 g, 4.27 mmol). Dry THF (20 mL) was added, and the solution was cooled to −78 °C under argon. A solution of *n*-BuLi (2.45 M in hexanes, 2.1 mL, 5.11 mmol) was added dropwise, producing a very thick mixture that was difficult to stir. The mixture was maintained at −78 °C for 15 min and then warmed to 0 °C for 40 min. The mixture containing the mixed anhydride was cooled again to −78 °C, and then the 0 °C solution of lithiated oxazolidinone was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 30 min and then at 0 °C for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated to give the crude product that was purified by flash chromatography ($SiO_2$ 53 g, 10−25% EtOAc/hexanes) to provide **20** as a very viscous amber oil (0.829 g, 60%): TLC $R_f =$ 0.39 (1:2 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.59 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H), 7.16 (m, 1H), 7.05 (m, 1H), 6.89 (m, 1H), 4.45 (m, 1H), 4.40 (AB d, $J = 15.2$ Hz, 1H), 4.29 (AB d, $J = 15.2$ Hz, 1H), 4.25 (m, 1H), 4.19 (dd, $J = 9.2$, 3.1 Hz, 1H), 3.85 (s, 3H), 2.37 (m, 1H), 0.89 (d, $J = 7.1$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.8, 159.9, 153.9, 142.7, 140.7, 135.4, 128.6, 127.4, 127.1, 121.0, 113.9, 111.7, 63.2, 58.5, 55.2, 41.5, 28.2, 17.8, 14.5; IR (neat, KBr, $cm^{-1}$) 2964, 1767, 1697, 1593, 1218, 1061, 766; HRMS (FAB, $M^+$) *m/z* 353.1626 (calculated for $C_{21}H_{23}NO_4$, 353.1627).

**(*R*)-4-Isopropyl-3-(2-(3-methoxy-5-phenylphenyl)acetyl)oxazolidin-2-one (21).** To a solution of carboxylic acid **19** (1.0 g, 4.13 mmol) in dry THF (25 mL) was added $Et_3N$ (0.92 mL, 6.61 mmol). The solution was cooled to −78 °C, and pivolyl chloride (0.56 mL,

4.54 mmol) was added dropwise. A precipitate formed, and the mixture was stirred an additional 15 min at −78 °C and then at 0 °C for 1 h. In a separate flame-dried round-bottomed flask was added the Evans (*R*)-isopropyloxazoldinone (0.490 g, 3.79 mmol). Dry THF (20 mL) was added, and the solution was cooled to −78 °C under argon. A solution of *n*-BuLi (2.3 M in hexanes, 1.81 mL, 4.13 mmol) was added dropwise, producing a very thick mixture that was difficult to stir. The mixture was maintained at −78 °C for 15 min and then warmed to 0 °C for 40 min. The mixture containing mixed anhydride was cooled again to −78 °C, and then the 0 °C solution of lithiated oxazolidinone was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 30 min and then at 0 °C for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were washed with brine dried over sodium sulfate and concentrated to give the crude product that was purified by flash chromatography ($SiO_2$ 40 g, 15% EtOAc/hexanes) to provide **21** as a very viscous amber oil (0.632 g, 47%): TLC $R_f$ = 0.39 (1:2 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H), 7.15 (m, 1H), 7.04 (m, 1H), 6.88 (m, 1H), 4.45 (m, 1H), 4.39 (AB d, $J$ = 15.2 Hz, 1H), 4.29 (AB d, $J$ = 15.2 Hz, 1H), 4.26 (m, 1H), 4.20 (dd, $J$ = 9.2, 3.1 Hz, 1H), 3.85 (s, 3H), 2.38 (m, 1H), 0.89 (d, $J$ = 7.0 Hz, 3H), 0.82 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.9, 160.0, 153.9, 142.7, 140.8, 135.4, 128.6, 127.4, 127.2, 121.1, 114.0, 111.9, 63.2, 58.5, 55.3, 41.6, 28.2, 17.9, 14.5; IR (neat, KBr, $cm^{-1}$) 2964, 1768, 1695, 1593, 1215, 1059, 764; HRMS (FAB, $M^+$) $m/z$ 353.1628 (calculated for $C_{21}H_{23}NO_4$, 353.1627).

**(*S*)-4-Isopropyl-3-((*S*)-2-(3-methoxy-5-phenylphenyl)propanoyl)-oxazolidin-2-one (22).** To a −78 °C solution of biphenyloxazolidinone **20** (0.829 g, 2.34 mmol) in dry THF (23 mL) under argon was added a solution of LHMDS (1 M in THF, 3 mL, 3 mmol). The yellow-orange solution was stirred for 1 h at −78 °C. Then methyliodide (0.59 mL, 9.45 mmol) was added dropwise. Following 5 min the mixture was warmed to 0 °C and stirred an additional 1 h. Saturated ammonium chloride (20 mL) was added and the mixture warmed to ambient temperature. The mixture was diluted with ethyl acetate (20 mL), and the organic phase was separated. The aqueous phase was extracted with additional ethyl acetate (2 × 15 mL), and the combined organic phases were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated to provide the crude oil that was purified by flash chromatography ($SiO_2$ 43 g, 10% EtOAc/hexanes) to afford alkylated product **22** as a clear viscous oil and a single diastereomer (0.657 g, 76%): TLC $R_f$ = 0.63 (1:2 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.42 (m, 2H), 7.34 (m, 1H), 7.19 (m, 1H), 7.02 (m, 1H), 6.93 (m, 1H), 5.22 (q, $J$ = 7.0 Hz, 1H), 4.38 (m, 1H), 4.18 − 4.09 (m, 2H), 3.86 (s, 3H), 2.46 (m, 1H), 1.57 (d, $J$ = 7.0 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.4, 160.0, 153.6, 142.8, 142.1, 140.9, 128.7, 127.4, 127.2, 119.6, 112.7, 111.8, 63.1, 59.0, 55.3, 43.0, 28.5, 19.7, 18.0, 14.7; IR (neat, KBr, $cm^{-1}$) 3034, 2966, 1776, 1697, 1593, 1204, 1055, 763; HRMS (FAB, $M^+$) $m/z$ 367.1796 (calculated for $C_{22}H_{25}NO_4$, 367.1784).

**(*R*)-4-Isopropyl-3-((*R*)-2-(3-methoxy-5-phenylphenyl)propanoyl)-oxazolidin-2-one (23).** To a −78 °C solution of biphenyloxazolidinone **21** (0.471 g, 1.33 mmol) in dry THF (13 mL) under argon was added a solution of LHMDS (1 M in THF, 1.67 mL, 1.67 mmol). The yellow-orange solution was stirred for 1 h at −78 °C. Then methyl iodide (0.35 mL, 5.61 mmol) was added dropwise. Following 5 min the mixture was warmed to 0 °C and stirred an additional 0.5 h. Saturated ammonium chloride (20 mL) was added and the mixture warmed to ambient temperature. The mixture was diluted with ethyl acetate (20 mL), and the organic phase was separated. The aqueous phase was extracted with additional ethyl acetate (2 × 15 mL), and the organic phases were combined, washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated to provide the crude oil that was purified by flash chromatography ($SiO_2$ 24 g, 10% EtOAc/hexanes) to afford alkylated product **23** as a clear viscous oil and a single diastereomer (0.285 g, 58%): TLC $R_f$ = 0.63 (1:2 EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.43 (m, 2H), 7.34 (m, 1H), 7.19 (m, 1H), 7.02 (dd, $J$ = 2.4, 1.6 Hz, 1H), 6.92 (m, 1H), 5.21 (q, $J$ = 7.0 Hz, 1H), 4.38 (m, 1H), 4.20−4.09 (m, 2H), 3.86 (s, 3H), 2.46 (m, 1H), 1.56 (d, $J$ = 7.0 Hz, 3H), 0.93 (d, $J$ = 7.1 Hz, 3H), 0.92 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.4, 160.0, 153.6, 142.8, 142.1, 140.9, 128.7, 127.4, 127.2, 119.6, 112.7, 111.8, 63.1, 59.0, 55.3, 43.0, 28.5, 19.7, 18.0, 14.7; IR (neat, KBr, $cm^{-1}$) 2966, 2837, 1771, 1695, 1456, 1227, 1053, 762; HRMS (FAB, $M^+$) $m/z$ 367.1794 (calculated for $C_{22}H_{25}NO_4$, 367.1784).

**(*S*)-2-(3-Methoxy-5-phenylphenyl)propan-1-ol.** To a 0 °C solution of methyloxazolidinone **22** (0.228 g, 0.621 mmol) in dry THF (10 mL) under argon was added LAH (0.071 g, 1.87 mmol) in one portion. Following 1 h, the reaction was quenched by the careful sequential addition of 0.07 mL of water, 0.14 mL of 4 N NaOH, and 0.07 mL of water. The mixture was stirred for 15 min at ambient temperature, and the solids were filtered (celite) and rinsed with ether. The filtrate was concentrated and the residue purified by flash chromatography ($SiO_2$ 11 g, 10−25% EtOAc/hexanes) to afford the alcohol as a clear viscous oil (0.122 g, 81%): TLC $R_f$ = 0.3 (1:2 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 7.06 (m, 1H), 7.00 (m, 1H), 6.79 (m, 1H), 3.87 (s, 3H), 3.75 (m, 2H), 3.00 (hex, $J$ = 6.9 Hz, 1H), 1.38 (t, $J$ = 6.2 Hz, 1H), 1.32 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.2, 145.7, 143.0, 141.2, 128.7, 127.5, 127.2, 119.0, 112.3, 110.9, 68.6, 55.3, 42.7, 17.6; IR (neat, KBr, $cm^{-1}$) 3371, 3059, 2961, 1593, 1462, 1213, 1022, 764; HRMS (FAB, $M^+$) $m/z$ 242.1311 (calculated for $C_{16}H_{18}O_2$, 242.1307).

**(*R*)-3-(3-Methoxy-5-phenylphenyl)-1,1-dibromobutene (24).** To a 0 °C solution of previously synthesized alcohol (0.285 g, 1.17 mmol) in dry $CH_2Cl_2$ (14 mL) was added Dess−Martin periodinate (0.748 g, 1.76 mmol) in a single portion. The mixture was stirred at 0 °C for 1 h, then was diluted with a 1:1 mixture of saturated aqueous $NaHCO_3$ and 20% $Na_2S_2O_3$ (20 mL). The biphasic mixture was stirred until all solids were dissolved. Then the organic phase was separated and the aqueous phase was extracted with two additional portions of $CH_2Cl_2$ (15 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated to afford the crude aldehyde that was used immediately in the next step.

To a 0 °C solution of $CBr_4$ (1.16 g, 3.5 mmol) in dry $CH_2Cl_2$ (28 mL) was added $PPh_3$ (1.84 g, 7.0 mmol) in a single portion. The resulting dark-yellow solution was stirred a further 5 min. Then the crude aldehyde dissolved in $CH_2Cl_2$ (5 mL) was added dropwise. The now wine-red solution was stirred for 30 min and then poured into ice cold ether (150 mL), producing a white precipitate. The mixture was filtered through a column of silica gel (20 g) equilibrated with hexanes and rinsed with hexanes until product elution ceased. The filtrate was concentrated and the residue purified by flash chromatography ($SiO_2$ 30 g, 2% EtOAc/hexanes) to afford dibromoalkene **24** as a clear viscous oil (0.409 g, 88% 2 steps): TLC $R_f$ = 0.52 (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.62 (m, 2H), 7.48 (m, 2H), 7.39 (m, 1H), 7.09 (m, 1H), 7.03 (m, 1H), 6.82 (m, 1H), 6.59 (d, $J$ = 9.5 Hz, 1H), 3.90 (s, 3H), 3.84 (dq, $J$ = 9.5, 7.0 Hz, 1H), 1.47 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.2, 144.9, 143.1, 142.5, 141.1, 128.7, 127.5, 127.2, 118.4, 111.9, 110.9, 88.7, 55.3, 43.6, 20.1; IR (neat, KBr, $cm^{-1}$) 2966, 1593, 1337, 1213, 1053, 762; HRMS (FAB, $M^+$) $m/z$ 393.9595 (calculated for $C_{17}H_{16}Br_2O$, 393.9568).

**(*R*)-2-(3-Methoxy-5-phenylphenyl)propan-1-ol.** To a 0 °C solution of methyloxazolidinone **23** (0.285 g, 0.776 mmol) in dry THF (10 mL) under argon was added LAH (0.089 g, 2.34 mmol) in one portion. Following 1.5 h, the reaction was quenched by the careful sequential addition of 0.09 mL of water, 0.18 mL of 4 N NaOH, and 0.09 mL of water. The mixture was stirred for 15 min at ambient temperature, and the solids were filtered (Celite) and rinsed with ether. The filtrate was concentrated and the residue purified by flash chromatography ($SiO_2$ 14 g, 10−15% EtOAc/hexanes) to afford the alcohol as a clear viscous oil (0.175 g, 93%): TLC $R_f$ = 0.3 (1:2 EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.59 (m, 2H), 7.44 (m, 2H), 7.36 (m, 1H), 7.07 (m, 1H), 7.01 (m, 1H), 6.80 (m, 1H), 3.87 (s, 3H), 3.75 (m, 2H), 3.01 (h, $J$ = 6.9 Hz, 1H), 1.46

(m, 1H), 1.32 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.2, 145.7, 143.0, 141.1, 128.7, 127.4, 127.2, 119.0, 112.3, 110.9, 68.6, 55.3, 42.7, 17.6; IR (neat, KBr, cm$^{-1}$) 3371, 3058, 2961, 1593, 1454, 1215, 1020, 764; HRMS (FAB, $M^+$) *m/z* 242.1295 (calculated for $C_{16}H_{18}O_2$, 242.1307).

**(*S*)-3-(3-Methoxy-5-phenylphenyl)-1,1-dibromobutene (25).** To a 0 °C solution of the previously synthesized alcohol (0.175 g, 0.722 mmol) in dry $CH_2Cl_2$ (9 mL) was added Dess−Martin periodinate (0.459 g, 1.08 mmol) in a single portion. The mixture was stirred at 0 °C for 1.5 h, then was diluted with a 1:1 mixture of saturated aqueous $NaHCO_3$ and 20% $Na_2S_2O_3$ (20 mL). The biphasic mixture was stirred until all solids were dissolved. Then the organic phase was separated and the aqueous phase was extracted with two additional portions of $CH_2Cl_2$ (10 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated to afford the crude aldehyde that was used immediately in the next step.

To a 0 °C solution of $CBr_4$ (0.718 g, 2.17 mmol) in dry $CH_2Cl_2$ (18 mL) was added $PPh_3$ (1.14 g, 4.35 mmol) in a single portion. The resulting dark-yellow solution was stirred a further 5 min, and then the crude aldehyde dissolved in $CH_2Cl_2$ (2 mL) was added dropwise. The now wine-red solution was stirred for 40 min and then poured into ice cold ether (150 mL), producing a white precipitate. The mixture was filtered through a column of silica gel (15 g) equilibrated with hexanes and rinsed with hexanes until product elution ceased. The filtrate was concentrated and the residue purified by flash chromatography ($SiO_2$ 18 g, 2% EtOAc/hexanes) to afford dibromoalkene **25** as a clear viscous oil (0.216 g, 76% two steps): TLC $R_f = 0.52$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.59 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.07 (m, 1H), 7.01 (dd, $J = 2.3$, 1.6 Hz, 1H), 6.80 (m, 1H), 6.56 (d, $J = 9.5$ Hz, 1H), 3.88 (s, 3H), 3.81 (dq, $J = 9.5$, 7.0 Hz, 1H), 1.45 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.2, 145.0, 143.2, 142.5, 141.1, 128.7, 127.5, 127.3, 118.4, 111.9, 110.9, 88.7, 55.4, 43.6, 20.1; IR (neat, KBr, cm$^{-1}$) 2966, 1593, 1456, 1339, 1213, 1053, 762; HRMS (FAB, $M^+$) *m/z* 393.9580 (calculated for $C_{17}H_{16}Br_2O$, 393.9568).

**(*S*)-3-(3-Methoxy-5-phenylphenyl)butyne (26).** To the dibromoalkene **24** (0.099 g, 0.25 mmol) in an 8 mL screw cap vial was added magnesium (0.012 g, 0.50 mmol) and dry THF (0.25 mL). The vial was sealed tightly with a rubber septum and flushed with argon. The mixture was heated in a 75 °C oil bath for 2.5 h when a check by TLC showed consumption of the starting material. The mixture was cooled and the residue purified by flash chromatography ($SiO_2$ 6 g, 5% EtOAc/hexanes) to afford acetylene **26** as a clear viscous oil (0.057 g, 96%): TLC $R_f = 0.44$ (5% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.59 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 7.20 (m, 1H), 7.00 (dd, $J = 2.4$, 1.6 Hz, 1H), 6.96 (m, 1H), 3.88 (s, 3H), 3.81 (dq, 7.1, 2.5 Hz, 1H), 2.29 (d, $J = 2.5$ Hz, 1H), 1.56 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.1, 144.6, 143.0, 141.1, 128.7, 127.5, 127.2, 118.4, 111.6, 111.2, 86.9, 70.3, 55.4, 31.8, 24.2; IR (neat, KBr, cm$^{-1}$) 3292, 2976, 1595, 1335, 1213, 1049, 764; HRMS (FAB, $M^+$) *m/z* 236.1222 (calculated for $C_{17}H_{16}O$, 236.1201).

**(*R*)-3-(3-Methoxy-5-phenylphenyl)butyne (27).** To the dibromoalkene **25** (0.228 g, 0.573 mmol) in an 8 mL screw cap vial was added magnesium (0.028 g, 1.16 mmol) and dry THF (0.6 mL). The vial was sealed tightly with a rubber septum and flushed with argon. The mixture was heated in a 75 °C oil bath for 2 h when a check by TLC showed consumption of the starting material. The mixture was cooled and the residue purified by flash chromatography ($SiO_2$ 13 g, 5% EtOAc/hexanes) to afford acetylene **27** as a clear oil (0.132 g, 97%): TLC $R_f = 0.44$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.62 (m, 2H), 7.46 (m, 2H), 7.38 (m, 1H), 7.24 (m, 1H), 7.04 (m, 1H), 6.99 (m, 1H), 3.90 (s, 3H), 3.84 (dq, $J = 7.1$, 2.5 Hz, 1H), 2.32 (d, $J = 2.5$ Hz, 1H), 1.59 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.1, 144.6, 143.0, 141.1, 128.7, 127.4, 127.2, 118.4, 111.6, 111.2, 86.9, 70.4, 55.3, 31.8, 24.2; IR (neat, KBr, cm$^{-1}$) 3294, 2976, 1595, 1334, 1213, 1049, 764; HRMS (FAB, $M^+$) *m/z* 236.1204 (calculated for $C_{17}H_{16}O$, 236.1201).

**2,4-Diamino-5-[(*S*)-3-(3-methoxy-5-phenylphenyl)but-1-ynyl]-6-methylpyrimidine (*S*-10a).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.052 g, 0.208 mmol), $Pd(PPh_3)_2Cl_2$ (0.011 g, 0.016 mmol), CuI (0.005 g, 0.026 mmol), and alkyne **26** (0.098 g, 0.413 mmol) were reacted in DMF/$Et_3N$ (1 mL each) at 60 °C for 2 h. Following the general workup procedure flash chromatography ($SiO_2$ 10 g, 2% MeOH/$CHCl_3$) afforded coupled pyrimidine *S*-**10a** as a pale solid (0.073 g, 97%, 98% ee). An analytical sample was generated by triturating in ether. TLC $R_f = 0.22$ (EtOAc); mp 140.2−141.5 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58 (m, 2H), 7.44 (m, 2H), 7.35 (m, 1H), 7.24 (m, 1H), 7.02 (m, 1H), 6.99 (m, 1H), 5.11 (bs, 2H), 4.82 (bs, 2H), 4.08 (q, $J = 7.1$ Hz, 1H), 3.88 (s, 3H), 2.39 (s, 3H), 1.63 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.6, 164.1, 160.4, 160.2, 145.3, 143.1, 141.0, 128.8, 127.6, 127.2, 118.3, 111.5, 111.1, 101.8, 91.5, 75.7, 55.4, 33.2, 24.7, 22.9; HRMS (FAB, $M^+$) *m/z* 358.1779 (calculated for $C_{22}H_{22}N_4O$, 358.1794); HPLC (a) $t_R = 6.90$ min, 99.2%, (b) $t_R = 6.92$ min, 99.4%.

**2,4-Diamino-5-[(*R*)-3-(3-methoxy-5-phenylphenyl)but-1-ynyl]-6-methylpyrimidine (*R*-10a).** According to the general Sonagashira coupling procedure, iodopyrimidine **11** (0.071 g, 0.28 mmol), $Pd(PPh_3)_2Cl_2$ (0.014 g, 0.020 mmol), CuI (0.007 g, 0.037 mmol), and alkyne **27** (0.132 g, 0.559 mmol) were reacted in DMF/$Et_3N$ (1.3 mL each) at 50 °C for 2.5 h. Following the general workup procedure flash chromatography ($SiO_2$ 14 g, 2% MeOH/$CHCl_3$) afforded the coupled pyrimidine *R*-**10a** as a pale solid (0.095 g, 93%, 98% ee). An analytical sample was generated by triturating in ether. TLC $R_f = 0.22$ (EtOAc); mp 139.3−140.4 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$; $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.6, 164.1, 160.4, 160.2, 145.3, 143.1, 141.0, 128.8, 127.6, 127.2, 118.3, 111.5, 111.1, 101.8, 91.5, 75.7, 55.4, 33.2, 24.7, 22.9; HRMS (FAB, $M^+$) *m/z* 358.1790 (calculated for $C_{22}H_{22}N_4O$, 358.1794); HPLC (a) $t_R = 6.88$ min, 99.2%, (b) $t_R = 6.89$ min, 98.7%.

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**Supporting Information Available:** Details of HPLC purity determinations for compounds **10a−d**, *S*-**10a**, *R*-**10a**, **17a−d**, including instrumentation, tabulated data, and copies of chromatograms; details of % ee determinations for *S*-**10a**, *R*-**10a**; $^1$H NMR and $^{13}$C NMR spectra of compounds **5**, **7** to **10a−d**, **13**, **14** to **17a−d**, **18−27**, *S*-**10a**, *R*-**10a**, and appropriate intermediates; synthesis of boronic acid **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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