JOC Article

General Scope of 1,4-Diastereoselective Additions to a 2(3*H*)-Quinazolinone: Practical Preparation of HIV Therapeutics

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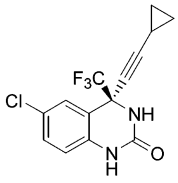
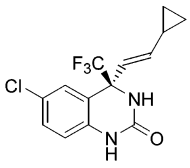
The practical and highly diastereoselective syntheses of CF_3-substituted dihydroquinazolinones via 1,4-additions of nucleophiles to chiral auxiliary substituted 2(3*H*)-quinazolinones is described. This methodology is applied to the syntheses of the NNRTIs (nonnucleoside reverse transcriptase inhibitors) DPC 961 (**1**) and DPC 083 (**2**), which are useful for the treatment of HIV (human immunodeficiency virus). The synthesis of DPC 961 (**1**) requires three steps, proceeds in >55% overall yield from the keto-aniline **9**, and gives synthetic access to DPC 083 (**2**). In addition, the scope of the new diastereoselective 1,4-addition chemistry is investigated. The first preparation of DPC 961 (**1**) described in this paper is a derivatization fractional crystallization protocol.

Introduction

Human immunodeficiency virus (HIV) is prone to mutation, which leads to drug resistance. In an effort to control mutant strains of the virus, new therapies are under constant development. DPC 961 (**1**) and DPC 083 (**2**) are nonnucleoside reverse transcriptase inhibitors (NNRTIs) that show promise for the treatment of HIV as well as new mutant strains of the virus.[1] To evaluate DPC 961 (**1**) and DPC 083 (**2**) as HIV NNRTIs, practical asymmetric syntheses of this class of dihydroquinazolinones was required.



1
DPC 961



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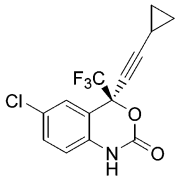
DPC 083



3
efavirenz
Sustiva™

Reduction of DPC 961 (**1**) with lithium aluminum hydride gives DPC 083 (**2**) in excellent yield,[1b] so our focus was directed toward the synthesis of DPC 961 (**1**).

Results and Discussion

We initially prepared DPC 961 (**1**) by a derivatization and fractional crystallization method, employing a camphanoyl auxiliary (Scheme 1).[2] The *p*-methoxybenzyl (PMB) protected ketoaniline **4** is a starting material for the commercial preparation of the HIV NNRTI efavirenz (Sustiva) **3**.[3] When **4** is reacted with KOCN in aqueous acetic acid at 60 °C, the hemiaminal **5** precipitates in high yield.[4] The hemiaminal **5** is dehydrated thermally in refluxing *m*-xylene, and the ketimine **6** crystallizes on cooling in good yield.

Addition of lithium cyclopropylacetylide occurs exclusively at the imino function of **6** in THF at −55 °C and

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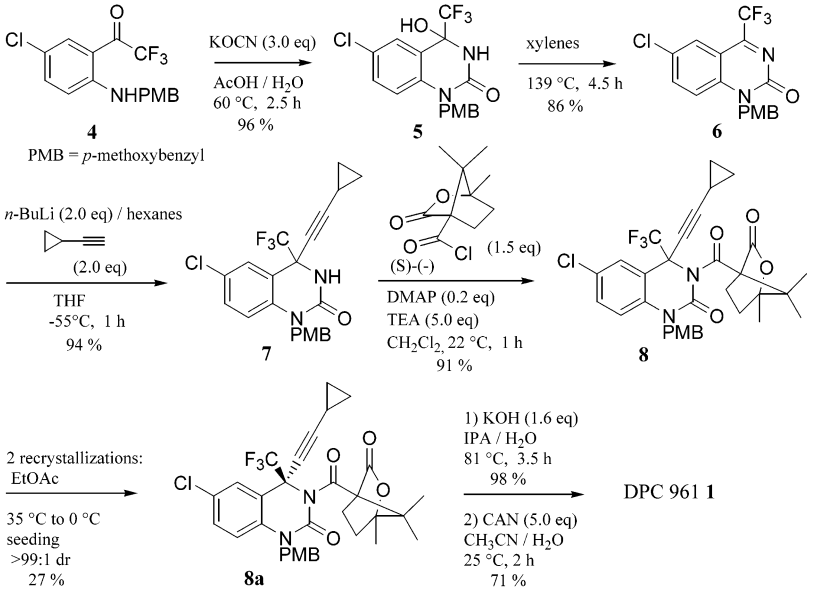
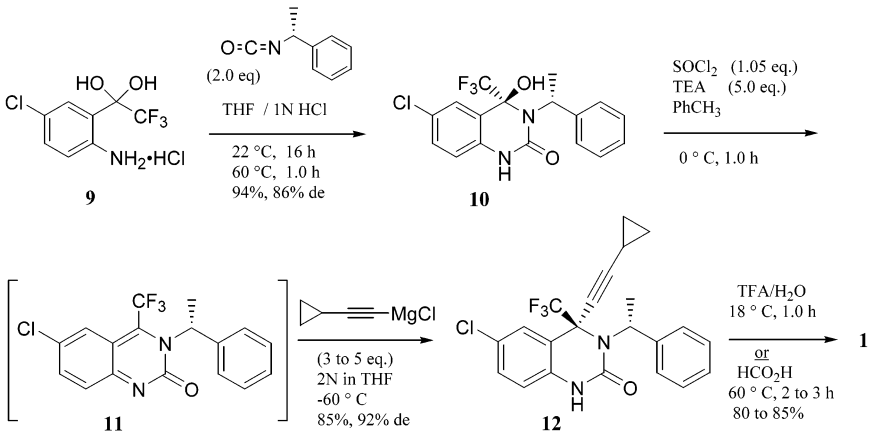
SCHEME 1



SCHEME 2



affords **7** in 94% yield. The PMB protecting group of **7** allows regioselective monoacylation with (*S*)-(−)-camphanic chloride to provide a diastereomeric mixture of **8** in 91% yield. Without PMB protection, the acylation is regiorandom and accompanied by bisacylation. Two fractional crystallizations of the diastereomeric mixture of **8** from ethyl acetate afford a 27% yield of the desired diastereomer **8a**. DPC 961 (**1**) could be obtained from **8a** in two steps by employing basic hydrolysis followed by oxidative debenzylation in 70% overall yield. However, the fractional crystallization was difficult to reproduce, volume inefficient, and required the expensive derivatizing agent (*S*)-(−)-camphanic chloride.

We recently reported a new diastereoselective 1,4-addition protocol that enables the synthesis of DPC 961 (**1**) (Scheme 2).[5]

The hydrate hydrochloride ketoaniline **9**[3] reacts with (*R*)-(+)-α-methylbenzyl isocyanate in THF containing 1 N HCl to give the hemiaminal **10** as a mixture of diastereomers in a ratio of 93:7. The absolute configuration of the major diastereomer of **10** was determined by X-ray crystallography and is shown in Scheme 2. The hemiaminal **10** is dissolved in a mixture of toluene and TEA (triethylamine) at 0 °C, and 1 equiv of thionyl chloride is added to generate intermediate **11**. Intermediate **11** is trapped at −60 °C by an excess of cyclopropylacetylene magnesium chloride (CPAMgCl) to give the dihydroquinazolinone **12**. At 95% conversion, the diastereomeric excess is consistently around 92%. The dihydroquinazolinone **12** is crystallized from methanol to afford an 85% isolated yield of the desired diastereomer exclusively (absolute configuration confirmed by X-ray). Exposure of **12** to wet TFA at 18 °C causes complete deprotection within 1 h, affording an 80% yield of DPC 961 (**1**).[6c] Formic acid at 60 °C also induces ionization of the phenethyl group to transform **12** into DPC 961 (**1**) in 85% yield.

Extended imines of type **11** (Scheme 2), known as substituted 2(3*H*)-quinazolinones, are reported to be

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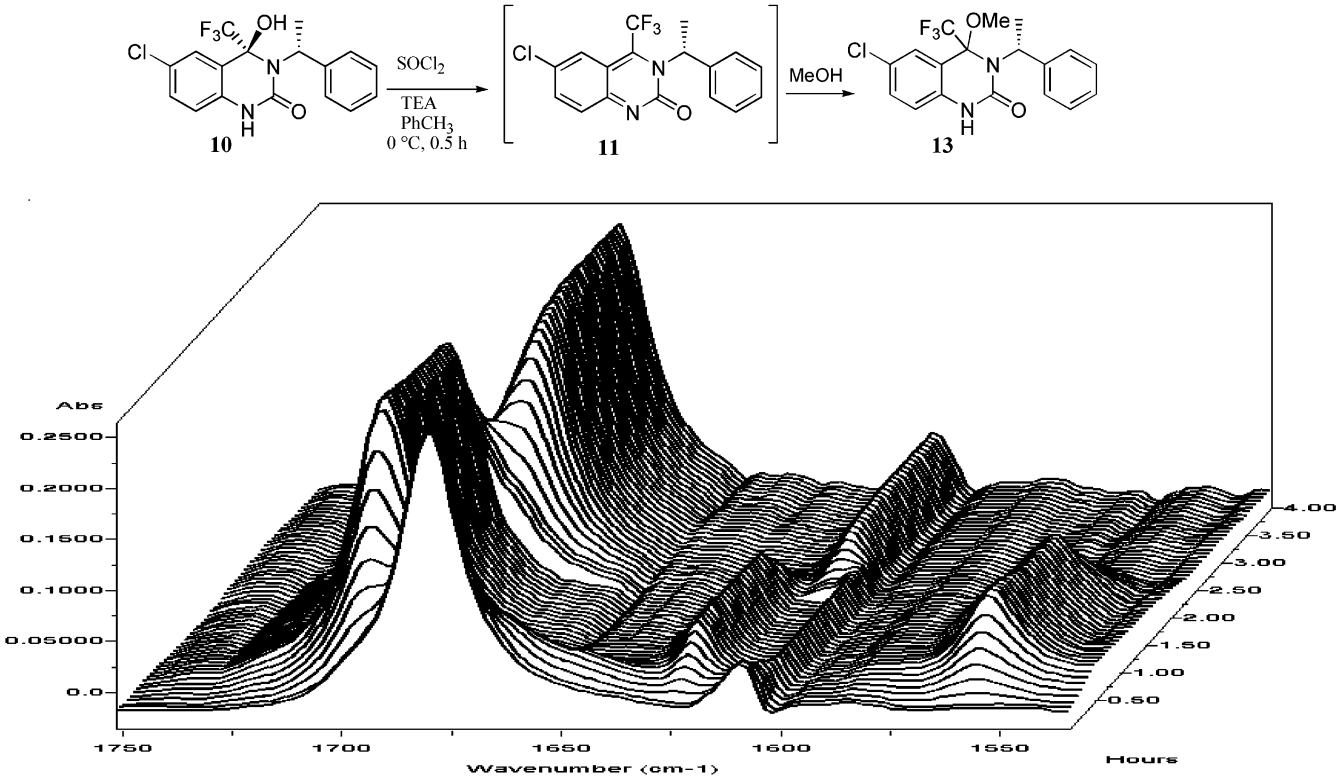

FIGURE 1. IR of **10** to **11** to **13**.

highly colored compounds ranging from yellow to red.[6] Although 2(3*H*)-quinazolinones have been isolated,[6a,c] this particular bright orange analogue bearing a trifluoromethyl group has proven too reactive for practical isolation. Eventually, we found that **11** could be produced in a mixture of CD_2Cl_2 and TEA-d_{15}, with trifluoromethanesulfonic anhydride as the dehydrating agent. The clear orange solution of **11** that resulted was stable for several hours at −5 °C and proved amenable to NMR characterization. The ^{19}F NMR spectrum of **10** showed a peak at −81.8 ppm, which shifted to −54.6 ppm when converted into **11**. The ^{13}C NMR spectrum of **10** has a CN peak at 85.1 ppm (q, $J_{CF} = 31$ Hz), which shifted to the aromatic region at 146.5 ppm (q, $J_{CF} = 33$ Hz) when converted into **11**. In addition, the ^{13}C NMR spectrum of **11** had an imine carbon signal at 160.4 ppm.

The intermediate **11** has also been generated with a ReactIR 1000 DiComp probe submerged into the reaction mixture (Figure 1). The absorption corresponding to the carbonyl of **10**, recorded at 1681 cm^{-1}, decreased during the addition of thionyl chloride giving a bright orange color, and a new absorption appeared at 1696 cm^{-1}, characteristic of the carbonyl present in **11**. The increased carbonyl absorption of 15 cm^{-1}, indicating a lessening mesomerism or more carbonyl characteristic, supports intermediate **11**. 1,4-Addition of methanol to intermediate **11** returned the carbonyl absorption to 1680 cm^{-1}, giving **13**, and the once bright orange mixture became colorless.

We examined the effect of lithium and magnesium as counterions to cyclopropylacetylide (CPA) with respect to the diastereoselectivity when reacted with 2(3*H*)-quinazolinone **11** (Table 1).

In addition, a variety of nucleophiles have been shown to add to **11** with good to excellent diastereoselectivity (Table 1, entries for **13**−**19**). The de's (diastereomeric excesses) and conversions to products for Table 1 were determined by HPLC. The major diastereomers of products **12** and **13** were isolated by crystallization, and the respective minor diastereomers were isolated by chromatography. In reactions for **14**−**18**, the diastereomers were separated by chromatography and fully characterized. Isolated yields were only measured for preparations of **12**. In some cases, about 1% nucleophilic addition occurred at the carbonyl of **11** to give α-methylbenzylimines as *E*−*Z* mixtures. For the phenyl additions, about half of the reaction mixture consisted of unknown byproducts.

11 also reacts diastereoselectively with enamines. The reaction of an enamine with an unsaturated imine to give an enamine adduct, especially diastereoselectively, appears to be unprecedented. It is related to the Michael and Stork reactions. A recent paper by Corey describes a Diels−Alder reaction of an enamine with an unsaturated imine. In the present case a Diels−Alder reaction is precluded by the fixed planarity of the bicyclic diene and probably steric factors. The enamine adduct was isolated and characterized (Scheme 3).[7]

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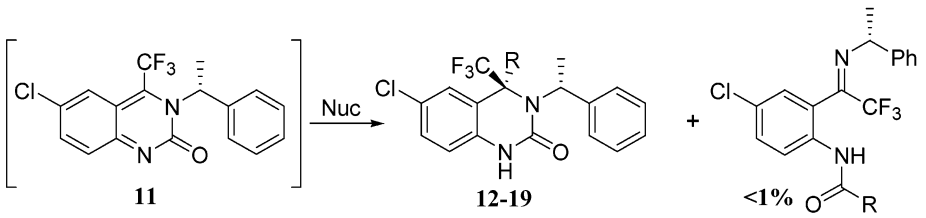
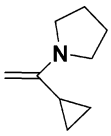
TABLE 1. Additions to 11



11 **12-19**

product	Nucleophile (Nuc)	Reaction temperature, °C	conversion to products	reaction de, %
12	CPAMgCl[a]	–60	95%	92
12	CPAMgCl[a]	–10	97%	80
12	CPALi[a]	–70	95%	85
13	CH_3OH	–5	97%	80
14	$CH_2{=}CH_2MgBr$	–60	88%	95
14	$CH_2{=}CH_2MgBr$	0	90%	70
15	PhMgCl	–60	35%	95
15	PhLi	–20	40%	40
16	$PhCH_2MgCl$	–60	93%	<10
17	CH_3MgI	–60	90%	55
17	CH_3ZnCl	–5	94%	85
18	$Li(^tBuO)_3AlH$	–60	94%	85 (R=H)
19		–60	89%	95

[a] CPA = cyclopropylacetylene.

Conclusions

In conclusion, the diastereoselectivity observed can be attributed to the asymmetric steric environment provided by the chiral auxiliary. Variations in diastereoselectivity are correlated with the reactivity of the nucleophile and reaction temperature. Solvent and concentration appear to have little effect on the diastereoselective outcome. There is no evidence for the involvement of chelation. As for the incipient chiral center, the larger of the two substituents tends to occupy the position behind the plane of the paper (using the *R*-phenethyl auxiliary). This

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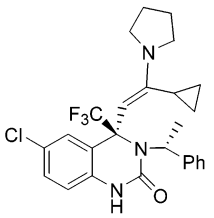
SCHEME 3



19

chemistry is amenable to multikilogram scale and proves to be a versatile way to prepare enantiopure dihydroquinazolinones.

Experimental Section

Melting points were taken by capillary tube apparatus or by DSC. Flash chromatography was performed using silica gel 60 (230−400 mesh). Accurate mass spectra were recorded (ESI-TOF-MS). Reagents and solvents were purchased and used as received. Reactions requiring anhydrous conditions were conducted in oven-dried glassware under an atmosphere of nitrogen unless otherwise noted. HPLC used a vareity of columns and methods: for example, Zorbax SB C-18, 3.5 μm, 15 cm× 4.6 mm, 50 °C, 254 nm, flow 1.0 mL/min A: H_2O (0.05% TFA) B: CH_3CN. 70% B, 4 min, to 99% at 7 min stop time 9.5 min. Retention times: **10**, 2.4 min; diastereomer of **10**, 2.3 min; toluene, 3.1 min; **12**, 5.9 min; diastereomer of **12**, 6.1 min; imine isomer of **12**, 5.5 min; methanol adducts of **11**, 3.7 min (**13**, major) and 4.5 min (**13**, minor).

Analogues **13**−**19** were prepared on the gram scale using the general procedure described to prepare **12**.

6-Chloro-4-hydroxy-1-[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (5). Compound **4** (250 g, 0.729 mol) was suspended in acetic acid/water (10:1, 1.46 L). The mixture was heated to 60 °C and KOCN (177.4 g, 2.19 mol) added with rapid stirring. After 3 h at 60 °C, the reaction was complete and cooled to 17 °C. The yellow solid was collected by filtration, rinsed with water (6 L), and dried in a vacuum oven at 80 °C to give **5** (277 g) in 98% yield: mp (DSC) (10 °C/min) onset 162.68 °C, peak 180.12 °C; IR (thin film/KBr) 3261, 1641, 1604, 1513, 1446 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.71 (3H, s), 5.02 (1H, d, J = 16.2 Hz), 5.15 (1H, d, J = 16.2 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.98 (1H, d, J = 9.0 Hz), 7.16 (2H, d, J = 8.6 Hz), 7.42 (1H, dd, J = 9.0, 2.0 Hz), 7.49 (1H, d, J = 2.0 Hz), 8.27 (1H, br s), 8.88 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.7, 54.9, 80.1 (q, J = 33 Hz), 113.9, 116.0, 119.9, 123.4 (q, J = 290 Hz), 125.6, 126.6, 127.5, 128.5, 130.7, 136.1, 150.8, 158.2 (C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −84.8; MS (CI+) calcd for 387.0723 $(M + H)^+$, found 387.0731. Anal. Calcd for $C_{17}H_{14}ClF_3N_2O_3$: C, 52.79; H, 3.65; N, 7.24. Found: C, 52.76; H, 3.59; N, 7.21.

6-Chloro-1-[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)hydroquinazolin-2-one (6). Compound **5** (269 g, 0.695 mol) was suspended in *m*-xylene (2.7 L) and heated at reflux to give a homogeneous mixture. Water was removed using a Dean−Stark trap. The reaction was complete after 4.0 h and cooled to 7 °C. The resulting yellow solid was collected by filtration and dried in a vacuum oven at 80 °C to afford **6** (220 g) in 86% yield. The mother liquor contains a mixture of **5** and **6** and can be recycled: mp (DSC) (10 °C/min) onset 147.44 °C, peak 148.11 °C; IR (thin film/KBr) 1671, 1620, 1553, 1514 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.72 (3H, s), 5.47 (2H, s), 6.88 (2H, d, J = 8.6 Hz), 7.29 (2H, d, J = 8.6 Hz), 7.67 (1H, d, J = 9.6 Hz), 7.88 (1H, s), 7.95 (1H, d, J = 9.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.7, 54.9, 112.3, 113.9, 118.3, 119.5 (q, J = 280 Hz), 124.3, 127.0, 127.46, 128.2, 136.5, 143.1, 153.3, 158.1 (N═C, q, J = 35 Hz), 158.5 (C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −65.9; MS (CI+) calcd for 369.0617 $(M + H)^+$, found 369.0604. Anal. Calcd for $C_{17}H_{12}ClF_3N_2O_2$: C, 55.37; H, 3.28; N, 7.60. Found: C, 55.06; H, 3.37, N, 7.54.

6-Chloro-4-(2-cyclopropylethynyl)-1-[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (7). *n*-Butyllithium (477 mL, 2.5 M in hexanes) was added to a solution of CPA (118.7 mL, 1.19 mol) in THF (2 L) at −50 °C. A solution of **6** (219 g, 0.593 mol) in THF (1 L) was added via cannula at −50 °C. The reaction was complete within 0.5 h. It was quenched with H_2O (1 L) and warmed to 22 °C. Extraction with ethyl acetate followed by precipitation with heptane gave **7** (225 g) in 94% yield (see conversion of **8a** to **7** for spectra).

Compound 8. To a solution of **7** (240 g, 0.552 mol) in CH_2Cl_2 (1.2 L) were added TEA (385 mL, 2.76 mol) and DMAP (4-(dimethylamino)pyridine) (13.5 g, 0.11 mol), followed by (1*S*)-(−)-camphanic chloride (179 g, 0.828 mol). The reaction was complete within 1 h. It was quenched with 10% aqueous citric acid (1 L), and the organic layer was shaken with 5% sodium bicarbonate (2 L). Ethyl acetate (300 mL) was added to the organic phase, and the organic layer was dried (Na_2SO_4). The solution was concentrated by rotory evaporation to 800 mL and the product allowed to crystallize for 15 h with stirring. The colorless crystalline solid weighed 310 g (from two crops), with a 91% yield.

1-({(4*S*)-6-Chloro-4-(2-cyclopropylethynyl)-1-[(4-methoxyphenyl)methyl]-2-oxo-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-3-yl}carbonyl)-4,7,7-trimethyl-3-oxabicyclo-[2.2.1]heptan-2-one [8a (Single Diastereomer)]. Compound **8** (50 g) was dissolved with heating in ethyl acetate (1.2 L). The solution was cooled to 9 °C, and seed crystals were added. It was then cooled to −5 °C for 0.5 h and filtered to give **8a** (13 g, 80% de). Recrystallization from ethyl acetate (140 mL) gave **8a** (6.8 g, > 99% de): mp (DSC) (10 °C/min) onset 226.71 °C, peak 235.18 °C; $[\alpha]^{25}_D$ −198.9 (c = 0.608, $CHCl_3$); IR (KBr pellet) 2938, 2248, 1792, 1735, 1692, 1513, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88−0.95 (7H, m), 1.08 (3H, s), 1.23 (3H, s), 1.38−1.45 (1H, m), 1.63−1.74 (1H, m), 1.89−1.96 (1H, m), 2.53−2.57 (2H, m), 3.78 (3H, s), 4.48 (1H, d, J = 16.2 Hz), 5.58 (1H, d, J = 16.2 Hz), 6.83 (1H, d, J = 8.6 Hz), 6.95 (2H, d, J = 9.1 Hz), 7.24 (1H, dd, J = 2.5, 8.6 Hz), 7.42 (2H, d, J = 9.1 Hz), 7.69 (1H, d, J = 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.5, 8.2, 8.4, 9.7, 16.4, 17.4, 29.4, 33.4, 47.9, 55.2, 57.6, 65.1, 93.9, 97.4, 114.5, 116.8, 120.7, 123.2 (q, J = 290 Hz), 127.3, 127.5, 128.8, 129.0, 130.9, 136.5, 150.6, 159.1 (C═O), 171.9 (C═O), 177.7 (C═O); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.2; MS (CI+) calcd for 614.1795 $(M + H)^+$, found 614.1780. Anal. Calcd for $C_{32}H_{30}ClF_3N_2O_5$: C, 62.49; H, 4.92; N, 4.55. Found: C, 62.36; H, 4.72; N, 4.45.

Compound 7 (Single Enantiomer)]. Compound **8a** (20.6 g, 0.033 mol) was dissolved in *i*-PrOH (200 mL), and aqueous KOH (3.0 g, 0.054 mol, in 10 mL H_2O) added. The reaction was complete after 2.5 h at reflux. Water and ethyl acetate were added. The ethyl acetate layer was washed thoroughly with water and rotary evaporated to give **7** (15 g, estimated yield 98%) as a solidified foam. A sample was recrystallized from ethyl acetate for characterization: mp (DSC) (10 °C/min) onset 146.09 °C, peak 147.81 °C; $[\alpha]^{25}_D$ −31.6 (c = 0.600, MeOH); IR (KBr pellet) 3203, 3086, 2933, 2247, 1683, 1604, 1513 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.74−0.76 (2H, m), 0.88−0.90 (2H, m), 1.48−1.54 (1H, m), 3.69 (3H, s), 4.94 (1H, d, J = 16.2 Hz), 5.12 (1H, d, J = 16.2 Hz), 6.87 (2H, d, J = 8.6 Hz), 6.96 (1H, d, J = 9.0 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.41 (1H, dd, J = 2.5, 9.0 Hz), 7.46 (1H, bs), 8.97 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ −1.2, 8.1, 8.2, 43.8, 54.9, 57.6 (q, J = 33 Hz), 67.9, 91.7, 113.9, 116.5, 117.0, 123.8 (q, J = 290 Hz), 125.8, 127.4, 127.6, 128.3, 130.7, 136.5, 151.0, 158.2 (C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −81.2; MS (CI+) calcd for 435.1087 $(M + H)^+$, found 435.1084. Anal. Calcd for $C_{22}H_{18}ClF_3N_2O_2$: C, 60.77; H, 4.17; N, 6.44. Found: C, 60.52; H, 4.29; N, 6.37.

(4*S*)-6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (1). Compound **7**

(1.0 g, 0.023 mol) was dissolved in 10% aqueous CH_3CN (10 mL), and ceric ammonium nitrate (6.3 g, 0.011 mol) was added. After stirring for 3.5 h at 23 °C, the reaction mass was loaded directly onto a plug of silica gel and eluted with EtOAc. The fractions containing product were combined and the solvent removed in vacuo to give **1** (51 mg, 71% yield) (see conversion of **12** to **1** for spectra).

3-((1*R*)-1-Phenylethyl)-(4S)-6-chloro-4-hydroxy-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (10). Compound **9** (21 kg, 75 mol) was dissolved in THF (105 L), and water (7 L) and 37% HCl (0.6 L, 7.3 mol) were added. After 0.5 h, the solution was cooled to 0−5 °C. (*R*)-(+)-α-methylbenzyl isocyanate (22.2 kg, 150 mol, 96% ee) was added slowly while 0−5 °C was maintained. The mixture was stirred for 3 h at 10−15 °C and then for 12 h or longer at 18−20 °C until consumption of the isocyanate was complete. Carbon dioxide evolved slowly due to competing hydrolysis of the isocyanate. If unreacted isocyanate remains at isolation, it forms symmetrical urea by reaction with α-methylbenzylamine, which contaminates the product. The mixture was stirred for 2 h at 60−65 °C to complete ring closure. Water (53 L) and toluene (42 L) were added to the reaction. The organic layer was washed with water and distilled at 60−65 °C under reduced pressure until all of the water and THF were removed, and a final volume of 100 L was reached. The reaction was cooled to 0−5 °C for 2 h, filtered, rinsed with cold toluene, and dried in a vacuum oven at 70−90 °C to constant weight. The yield of **10** was 90% (25 kg) of high purity, high ee product of about 88% de. The filtrate was enriched in minor diastereomer and enantiomer. If the isocyanate used was >99% ee, heptane could be used for the isolation instead of toluene to give >95% yield and 86% de, with no enantioenrichment.

Compound 10 (major diastereomer): mp 240−250 °C (dec) (EtOAc); $[\alpha]^{25}_D$ +190 (*c* = 1.00 g/dL, EtOAc); IR (KBr) 3408, 3060, 2931, 2834, 1658, 1607 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (3H, d, *J* = 6.8 Hz), 5.24 (1H, q, *J* = 6.8 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.13−7.39 (5H, m, phenyl), 7.45 (1H, dd, *J* = 8.8 and 2.3 Hz), 7.50 (1H, s), 8.80 (1H, s), 9.90 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.9 (CH_3), 50.4 (NCH), 84.7 (q, *J* = 30 Hz), 115.8 (CH), 117.0, 124.0 (q, *J* = 290 Hz), 124.9, 126.3, 127.0, 127.9, 131.6, 136.0 (CCl), 143.3, 150.2 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −81.8 (s); MS (CI) calcd for $C_{17}H_{15}ClF_3N_2O_2$ (M + H) 371.0774, found 371.0764. Anal. Calcd for $C_{17}H_{14}ClF_3N_2O_2$: C, 55.07; H, 3.81; N, 7.56. Found: C, 55.33; H, 3.80; N, 7.51.

Compound 10 (minor diastereomer): isolated from the liquors by silica gel step-gradient chromatography using 0−18% EtOAc−CH_2Cl_2; $[\alpha]^{25}_D$ +4.5 (*c* = 1.92, EtOAc); ^1H NMR (300 MHz, DMSO-d_6) δ 1.75 (3H, d, *J* = 7.0 Hz), 5.34 (1H, q, *J* = 7.0 Hz), 6.97 (1H, d, *J* = 9.2 Hz), 7.06−7.38 (5H, m), 7.48 (1H, dd, *J* = 9.2 and 2.4 Hz), 7.50 (1H, s), 8.8 (1H, s), 9.9 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.7 (CH_3), 51.7 (CH), 85.1 (q, *J* = 31 Hz), 115.8 (CH), 117.3, 123.8 (q, *J* = 290 Hz), 125.0, 125.6 (CH), 126.2 (CH), 127.7 (CH), 127.8 (CH), 131.6 (CH), 136.2 (CCl), 142.7, 150.0 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −82.0 (s); MS (ESI) calcd for $C_{17}H_{15}ClF_3N_2O_2$ (M + H) 371.0774, found 371.0786.

General Reaction Method for the Diastereoselective Step. 3-((1*R*)-1-Phenylethyl)-6-chloro-4-(trifluoromethyl)-3-hydroquinazolin-2-one (11). Under N_2, the hemiaminal **10** (8.0 kg, 21.5 mol) was suspended in toluene (80 L) and treated with triethylamine (TEA, dried over mol sieves) (11.0 kg, 108 mol) to give a colorless solution that was cooled to −5 to 0 °C, and thionyl chloride (2.7 kg, 22.5 mol) was added slowly while −5 to 0 °C was maintained. This produced **11** as a bright orange mixture with TEA hydrochloride salt as a precipitate. The reaction can be conveniently assessed by quenching a sample directly into MeOH and analyzing the mixture of **13** by HPLC.

After 1 h at 0 °C, the mixture is cooled to the desired reaction temperature and a nucleophile added.

Compound 11: IR (reaction mixture) 1696 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2, −5 °C) δ 2.06 (3H, d, *J* = 6.8 Hz, CH_3), 5.76 (1H, q, *J* = 6.8 Hz, NCH), 7.07−7.25 (5H, m, phenyl), 7.28 (1H, d, *J* = 9.4 Hz), 7.52 (1H, dd, *J* = 9.4 Hz, *J* = 2.2 Hz), 7.88 (1H, s), 8.31 (2H, s, NH, TEA-d_{15} triflate salt); ^{13}C NMR (125 MHz, CD_2Cl_2, −5 °C) δ 16.1 (CH_3), 63.2 (q, J_{CF} = 4.3 Hz, NCH), 113.4(C), 120.8 (q, J_{CF} = 320 Hz, triflate CF_3), 120.8 (q, J_{CF} = 280 Hz, CF_3), 123.1 (q, J_{CF} = 8.3 Hz, CH), 126.9 (Ph, ortho), 128.0 (Ph, para), 128.7 (Ph, meta), 129.5 (CH), 131.6 (CCl), 138.2 (Ph, C), 139.5 (CH), 146.5 (q, J_{CF} = 33.0 Hz, NC), 153.4 (C═O), 160.4 (C═N); ^{19}F NMR (376 MHz, CD_2Cl_2) δ −54.6 (CF_3), −79.5 (triflate CF_3 from H-TEA-d_{15} salt in solution).

3-((1*R*)-1-Phenylethyl)-(4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (12). After 1 h at 0 °C, the mixture of **11** (described above) was cooled to −60 °C. A 2 M cyclopropylacetylene magnesium chloride solution in THF (54 L, 108 mol) was added to the mixture slowly while−60 °C was maintained. The de of **12** in the crude reaction mixture was determined to be 92% by HPLC. The resulting reaction mixture was quenched into 12% aqueous citric acid (60 L). The organic phase was washed with water and concentrated via distillation at 80 °C to remove water and THF. The remaining toluene was exchanged for methanol by employing azeotropic distillation. This induced crystallization of the product **12** (7.7 kg, 86% yield) with excellent chemical and stereochemical purity. Note: If it was necessary to conserve the nucleophile, the tertiary amine HCl salt could be filtered out of the 2(3*H*)-quinazolinone **11** mixture (under inert conditions) prior to addition of nucleophile. *N*-methylmorpholine was the preferred tertiary amine to facilitate salt filtration. Accordingly, the nucleophile requirement was reduced to 1.5−2 equiv from 4 to 5 equiv.

Compound 12: mp 212 °C (EtOAc); $[\alpha]^{25}_D$ −59 (*c* = 1.06, EtOAc); IR (KBr) 3190, 3058, 2941, 2240, 1683, 1604, 1502 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (2H, br s), 0.94 (2H, m), 1.62 (1H, br s), 1.77 (3H, d, *J* = 6.8 Hz), 5.38 (1H, br, NCH), 6.97 (1H, d, *J* = 9.1 Hz), 7.18 (1H, m), 7.29 (4H, m), 7.49 (1H, d, *J* = 9.1 Hz), 7.49 (1H, s), 10.05 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ −1.2, 8.3, 8.4, 19.8, 57.4 (br, NCH), 64.6 (q, br, NC), 66.2, 96.0, 115.0, 115.8, 123.8 (q, *J* = 290 Hz), 125.0, 125.7, 125.8, 127.6, 127.9, 131.2, 136.2, 141.9, 150.0 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −78.4 (s); MS (ESI) calcd for $C_{22}H_{19}ClF_3N_2O$ (M + H) 419.1138, found 419.1145. Anal. Calcd for $C_{22}H_{18}ClF_3N_2O$: C, 63.09; H, 4.33; N, 6.69. Found: C, 63.31; H, 4.31; N, 6.70.

Compound 12 (minor diastereomer): isolated from the liquors by silica gel step-gradient chromatography using CH_2Cl_2/hexanes then purified using a column with *i*-PrOH/hexanes: mp 85−95 °C (MeOH/H_2O); $[\alpha]^{25}_D$ +360 (*c* = 1.04, EtOAc); IR (film) 3190, 3090, 2934, 2245, 1678, 1606, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (2H, m), 0.84 (2H, m), 1.36 (1H, m), 2.01 (3H, d, *J* = 6.8 Hz), 5.35 (1H, q, *J* = 6.8 Hz), 5.75 (1H, d, *J* = 8.5 Hz), 7.03 (1H, dd, *J* = 8.5 and 2.2 Hz), 7.26−7.45 (5H, m), 7.53 (1H, s), 9.40 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 8.4, 8.5, 16.7, 56.5, 65.9 (q, *J* = 32 Hz), 67.6, 95.8, 115.5, 123.8 (q, *J* = 290 Hz), 126.2, 126.3, 127.8, 128.8, 130.6, 135.0, 142.6, 152.4 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.6 (s); MS (ESI) calcd for $C_{22}H_{19}ClF_3N_2O$ (M + H) 419.1138, found 419.1146.

***N*-{2-[(3*R*)(1*Z*)-2-Aza-3-phenyl-1-(trifluoromethyl)but-1-enyl]-4-chlorophenyl}-3-cyclopropylprop-2-ynamide [imine isomer of 12 (*E*−*Z* mixture; 1:2 in $CDCl_3$, 1:1 in DMSO-d_6)]:** isolated from the above column; IR (film) 3169, 2966, 2224, 1660, 1637, 1624 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.6−1.6 (cyclopropyl), 1.16 and 1.50 (3H, d, *J* = 6.5 Hz, methyl), 4.24 and 4.36 (1H, q, *J* = 6.5 Hz, NCH), 6.82 (1H, m, aromatic), 7.07 (1H, d, *J* = 7.8 Hz), 7.2−7.5 (5H, m, phenyl), 7.65 (1H, m), 10.5 and 10.8 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1, 9, 24, 62, 70, 93, 119.5 (q, *J* = 280 Hz), 124, 126, 128, 129, 131, 133, 142, 151 (C═O), 152.5 (q, *J* = 35 Hz, C═N); ^{19}F NMR (282 MHz, DMSO-d_6) δ −66.6, −66.9; ^{19}F NMR

(282 MHz, $CDCl_3$) δ −71.6, −72.0; MS (ESI) calcd for $C_{22}H_{19}ClF_3N_2O$ (M + H) 419.1138, found 419.1156.

2 M Cyclopropylacetylene Magnesium Chloride in THF. 2 M *n*-Butylmagnesium chloride in THF (54 L, 108 mol) was heated to the reaction temperature of 35 °C, and CPA (7.8 kg, 118 mol) was added slowly while 30−39 °C was maintained. During the addition, butane was vented through a condenser with the temperature set just above its boiling point. After the addition, the solution was held for 2−3 h at 30−39 °C, cooled to 20 °C, and used within 15 h. Reaction completion was determined by analyzing the mixture for consumption of *n*-butylmagnesium chloride. Other Grignard reagents can be used.

The following are MeOH adducts.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-methoxy-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (13, major diastereomer): isolated by crystallization; mp 277 °C (acetonitrile); $[\alpha]^{25}_D$ −38 (*c* = 0.927, EtOAc); IR (film) 3200, 3087, 2966, 1679 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.84 (3H, d, *J* = 7.0 Hz), 3.35 (3H, s), 5.13 (1H, q, *J* = 7.0 Hz), 7.02 (1H, d, *J* = 9.0 Hz, aromatic), 7.12−7.31 (5H, m, phenyl), 7.34 (1H, s), 7.53 (1H, dd, *J* = 9.0 Hz, *J* = 2.0 Hz), 10.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.7, 52.4, 52.6, 90.8 (q, *J* = 30 Hz), 112.0, 116.6, 123.0 (q, *J* = 290 Hz), 125.6, 125.9, 126.6, 127.8, 132.4, 137.6, 142.8, 150.7 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −79.4; MS (ESI) calcd for $C_{18}H_{17}ClF_3N_2O_2$ (M + H) 385.0931, found 385.0934. Anal. Calcd for $C_{18}H_{16}ClF_3N_2O_2$: C, 56.19; H, 4.19; N, 7.28. Found: C, 56.12; H, 4.01; N, 7.16.

Compound 13 (minor diastereomer): isolated from the liquors by silica gel step-gradient chromatography using 5−14% EtOAc/hexanes; mp 202 °C (methylene chloride/heptane); $[\alpha]^{25}_D$ +43 (*c* = 1.08, EtOAc); IR (film) 3206, 3088, 2951, 1681 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (3H, d, *J* = 7.0 Hz), 2.99 (3H, s), 5.13 (1H, q, *J* = 7.0 Hz), 7.06 (1H, d, *J* = 8.4 Hz, aromatic), 7.15−7.38 (6H, m, aromatic), 7.53 (1H, dd, *J* = 8.4 Hz, *J* = 2.2 Hz, aromatic), 10.3 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 52.3, 52.9, 90.5 (q, *J* = 30 Hz), 112.5, 116.7, 123.5 (q, *J* = 290 Hz), 125.7, 126.5, 126.9, 127.7, 128.3, 132.4, 137.5, 142.9, 151.3 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −80.2; MS (ESI) calcd for $C_{18}H_{17}ClF_3N_2O_2$ (M + H) 385.0931, found 385.0947. Anal. Calcd for $C_{18}H_{16}ClF_3N_2O_2$: C, 56.19; H, 4.19; N, 7.28. Found: C, 56.21; H, 4.08; N, 7.25.

***N*-{2-[(3*R*)(1*Z*)-2-Aza-3-phenyl-1-(trifluoromethyl)but-1-enyl]-4-chlorophenyl}methoxycarboxamide [imine isomer of MeOH adduct (*E*−*Z* mixture; 1:2 in $CDCl_3$, 1:1 in DMSO-d_6)]:** isolated from the above column; IR (film) 3442, 3312, 2975, 1745, 1727, 1581, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 and 1.53 (3H, d, *J* = 6.4 Hz, methyl), 3.45 and 3.80 (3H, s, methoxy), 4.36 (1H, m(2q), NCH), 5.66 and 6.32 (1H, s, NH), 6.86 and 7.20 (1H, d, *J* = 2.5 Hz, aromatic), 7.15−7.37 (5H, m, phenyl), 7.50 (1H, dd, *J* = 8.9 and 2.5 Hz, aromatic), 7.95 and 8.00 (1H, d, *J* = 8.9 Hz, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24, 53, 63, 119.5 (q, *J* = 280 Hz), 123, 126.5, 127.5, 128.5, 131, 134, 142.8, 152 (q, *J* = 35 Hz, C═N), 153.5 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.7, −72.0; MS (ESI) calcd for $C_{18}H_{17}ClF_3N_2O_2$ (M + H) 385.0931, found 385.0924.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-(trifluoromethyl)-4-vinyl-1,3,4-trihydroquinazolin-2-one (14 major diastereomer; prepared with 1 M vinylmagnesium bromide in THF): purified by flash column with 1% *i*-PrOH/5% EtOAc/hexanes; $[\alpha]^{25}_D$ −29 (*c* = 1.03, EtOAc); IR (film) 3198, 3099, 2971, 1679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, d, *J* = 6.8 Hz), 4.95 (1H, q, *J* = 6.8 Hz), 5.66 (1H, dq, *J* = 17.5 Hz, J_{HF} = 2.1 Hz, vinyl CH_2), 5.76 (1H, d, *J* = 11.6 Hz, vinyl CH_2), 6.07 (1H, dd, *J* = 17.5 Hz, *J* = 11.6 Hz, vinyl CH), 6.44 (1H, dd, *J* = 8.3 Hz, *J* = 0.5 Hz, aromatic), 7.13 (1H, s), 7.15 (1H, dd, *J* = 8.3 Hz, *J* = 2.2 Hz), 7.17−7.37 (5H, m, phenyl), 8.88 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 57.3, 70.5 (q, *J* = 28 Hz), 115.3, 115.9, 121.6 (vinyl), 124.7 (q, *J* = 290 Hz), 126.0, 126.1, 126.5, 127.8, 129.5, 130.6, 132.9 (vinyl), 135.9 (CCl), 141.6, 152.3 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.8; MS (ESI) calcd for $C_{19}H_{17}ClF_3N_2O$ (M + H) 381.0982, found 381.0999.

Compound 14 (minor diastereomer): 60 area % by HPLC; not all NMR peaks could be resolved unambiguously; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (3H, d, *J* = 6.8 Hz), 4.90 (1H, q, *J* = 6.8 Hz), 5.70 (2H, m, vinyl CH_2), 5.97 (1H, m, vinyl CH), 6.10 (1H, d, *J* = 8.3 Hz, aromatic), 7.05 (1H, dd, *J* = 8.3 Hz, *J* = 2.2 Hz), 7.15 (1H, s), 7.2−7.4 (5H, m, phenyl), 10.0 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 56.5, 70.0 (q, *J* = 30 Hz), 115.8, 121.7, 125.8, 126.2, 128.1, 129.2, 130.7, 132.5, 136.0, 142.9, 153.5 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.7; MS (ESI) calcd for $C_{19}H_{17}ClF_3N_2O$ (M + H) 381.0982, found 381.0997.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-phenyl-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (15 Major Diastereomer; Prepared with 2 M Phenylmagnesium Chloride in THF and 1.8 M Phenyllithium in Cyclohexane:Diethyl Ether 7:3). The diastereomers were separated and purified by silica gel step-gradient chromatography using 10−20% EtOAc/hexanes (twice). Major diastereomer: $[\alpha]^{23}_D$ +13 (*c* = 1.05, EtOAc); IR (film) 3196, 3098, 2963, 1678, 1602, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (3H, d, *J* = 6.7 Hz), 4.38 (1H, q, *J* = 6.7 Hz), 6.51 [1H, s (significantly upfield from where it occurs in the other analogues because of anisotropropy from the nearby phenyl group)], 6.55 (1H, d, *J* = 9.0 Hz), 7.12 (1H, dd, *J* = 9.0 Hz, *J* = 2.0 Hz), 7.20 (1H, m), 7.35 (4H, m), 7.50 (5H, m), 9.10 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 58.2, 73.4 (q, *J* = 30 Hz), 115.1, 119.0, 125.0 (q, *J* = 290 Hz), 125.8, 126.1, 126.2, 127.6, 128.6, 129.2, 129.3, 130.2, 130.3, 135.4, 137.4, 141.7, 152.6 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.0; MS (ESI) calcd for $C_{23}H_{19}ClF_3N_2O$ (M + H) 431.1138, found 431.1148.

Compound 15 (minor diastereomer): further purified by preparative HPLC, C18 column, 75−100% CH_3CN/H_2O; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (3H, d, *J* = 6.9 Hz, methyl), 4.39 (1H, q, *J* = 6.9 Hz, NCH), 6.44 (1H, s), 6.58 (1H, d, *J* = 8.6 Hz), 6.95−7.31 (11H, m), 10.2 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH3), 59.0 (NCH), 73.2 (q, *J* = 28 Hz), 115.1 (CH), 119.6 (C), 125.8 (q, *J* = 290 Hz), 126.2 (C), 126.3 (CH), 127.1 (CH), 127.5 (CH), 129.1 (CH), 130.3 (CH), 135.6 (C), 136.5 (C), 142.6 (C), 153.9 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.6; MS (ESI) calcd for $C_{23}H_{19}ClF_3N_2O$ (M + H) 431.1138, found 431.1140.

The benzyl analogue **16** is an interesting case because of its unusually low selectivity. This was the only case where the anion is conjugated. The diastereomers were separated and purified by silica gel chromatography using 15% EtOAc/hexanes.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-benzyl-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (16, more polar diastereomer; prepared with 2 M benzylmagnesium chloride in THF): mp 85−105 °C ($MeOH/H_2O$); $[\alpha]^{25}_D$ −24 (*c* = 1.16, EtOAc); IR (film) 3205, 3092, 2980, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, d, *J* = 7.0 Hz), 3.73 and 3.96 (2H, ABq, *J* = 17.5 Hz, $PhCH_2$), 4.83 (1H, q, *J* = 7.0 Hz), 6.54 (1H, d, *J* = 8.0 Hz, aromatic), 7.08 (2H, m), 7.15−7.40 (10H, m), 9.20 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 35.5, 57.0, 69.1 (q, *J* = 30 Hz), 115.8, 126.5, 128.0, 128.9, 129.3, 130.9, 133.4, 136.0, 142.2, 153.6 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.1; MS (ESI) calcd for $C_{24}H_{21}ClF_3N_2O$ (M + H) 445.1295, found 445.1309.

Compound 16 (less polar diastereomer): mp 148−150 °C (heptane); $[\alpha]^{25}_D$ +100 (*c* = 1.03, EtOAc); IR (film) 3213, 3092, 2963, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (3H, d, *J* = 6.6 Hz), 3.68 and 3.92 (2H, ABq, *J* = 17.3 Hz, $PhCH_2$), 4.98 (1H, q, *J* = 6.6 Hz), 6.15 (1H, d, *J* = 8.5 Hz, aromatic), 6.74−7.01 (10H, m), 7.05 (1H, dd, *J* = 8.5 Hz, *J* = 2.2 Hz), 7.35 (1H, s), 9.97 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 35.4, 55.3, 69.0 (q, *J* = 28 Hz), 115.7, 116.1, 125.3, 125.6 (q, *J* = 290 Hz), 125.9, 126.5, 127.17, 127.24, 128.2, 128.5, 130.1, 130.6, 132.5, 136.1, 142.3, 153.7 (C═O); ^{19}F NMR (282

MHz, $CDCl_3$) δ −76.9; MS (ESI) calcd for $C_{24}H_{21}ClF_3N_2O$ (M + H) 445.1295, found 445.1300.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-methyl-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (17, Major (More Polar) Diastereomer; Prepared with 3 M Methylmagnesium Iodide in Diethyl Ether and 2 M Methylzinc Chloride in THF). The diastereomers were separated and purified by silica gel step-gradient chromatography using 15−28% EtOAc/hexanes: $[\alpha]^{25}_D$ −33 (*c* = 1.76, EtOAc); IR (KBr) 3203, 3094, 3058, 2940, 1675, 1602, 1505 cm^{-1}. NMR (400 MHz, DMSO-d_6) δ 1.76 (3H, d, *J* = 6.5 Hz), 2.07 (3H, br s), 5.16 (1H, br, NCH), 6.95 (1H, d, *J* = 8.6 Hz, aromatic), 7.15−7.35 (5H, m, phenyl), 7.40 (1H, dd, *J* = 8.6 Hz, *J* = 2.4 Hz), 7.60 (1H, s), 9.87 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.7 (br, CH_3), 21.0 (br, CH_3), 54.3 (br, NCH), 65.2 (q, *J* = 28 Hz), 115.8 (CH), 118.2 (br), 125.4, 125.8 (br, CH), 126.1 (q, *J* = 290 Hz, CF_3), 126.2 (CH), 127.6 (br, CH), 127.9 (CH), 130.7 (CH), 137.1 (CCl), 143.2, 151.3 (br, C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ -77.9; MS (ESI) calcd for $C_{18}H_{17}ClF_3N_2O$ (M + H) 369.0982, found 369.0990.

Compound 17 (minor diastereomer): $[\alpha]^{25}_D$ +180 (*c* = 0.557, EtOAc); IR (KBr) 3190, 3086, 3042, 2954, 1672, 1601, 1504 cm^{-1}. NMR (400 MHz, DMSO-d_6) δ 1.90 (3H, d, *J* = 6.6 Hz), 2.05 (3H, br s), 5.09 (1H, q, *J* = 6.6 Hz, NCH), 6.91 (1H, d, *J* = 8.6 Hz, aromatic), 7.14−7.30 (5H, m, phenyl), 7.41 (1H, dd, *J* = 8.6 Hz, *J* = 2.7 Hz), 7.66 (1H, s), 9.80 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.22 (CH_3), 19.26 (CH_3), 53.3 (NCH), 64.6 (q, *J* = 27 Hz), 115.8 (CH), 117.9, 125.4, 125.8 (CH), 126.2 (CH), 126.4 (q, *J* = 290 Hz, CF_3), 128.0 (CH), 128.3 (CH), 130.8 (CH), 137.0 (CCl), 143.7, 151.5 (C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −78.2; MS (ESI) calcd for $C_{18}H_{17}ClF_3N_2O$ (M + H) 369.0982, found 369.0992.

3-((1*R*)-1-Phenylethyl)-6-chloro-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (18, Major Diastereomer; Prepared with 1 M Li(tBuO)$_3$AlH in THF). The diastereomers were separated and purified by silica gel step-gradient chromatography using 10−20%EtOAc/hexanes: mp 140−143 °C (MeOH/H_2O); $[\alpha]^{25}_D$ −86 (*c* = 1.14, EtOAc); IR (film) 3205, 3090, 2944, 1679 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (3H, d, *J* = 7.2 Hz), 5.45 (1H, q, *J* = 7.5 Hz), 5.48 (1H, q, *J* = 7.2 Hz), 6.90 (1H, d, *J* = 9.2 Hz, aromatic), 7.1−7.4 (7H, m, aromatic), 9.92 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.1, 55.7, 55.9 (q, *J* = 32 Hz), 115.5, 115.8, 116.1, 125.1 (q, *J* = 290 Hz), 125.4, 126.8, 127.0, 127.7, 128.8, 137.6, 142.1, 153.7 (C═O); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.2 (d, *J* = 7.3 Hz); MS (ESI) calcd for $C_{17}H_{15}ClF_3N_2O$ (M + H) 355.0825, found 355.0825.

Compound 18 (minor diastereomer): further purified by preparative HPLC, C18 column, 75−100% MeOH/H_2O; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88 (3H, d, *J* = 7.04 Hz), 4.97 (1H, q, *J* = 7.04 Hz), 5.83 (1H, q, J_{HF} = 7.62 Hz), 6.96 (1H, d, *J* = 8.47 Hz, aromatic), 7.19−7.36 (5H, m, aromatic), 7.38, (1H, dd, *J* = 8.47, *J* = 2.40), 7.41 (1H, s), 9.74 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.9 (CH_3), 59.0 (NCH), 59.5 (q, *J* = 31 Hz, CH), 114.9, 115.8 (CH), 125.1 (q, *J* = 287 Hz), 125.2, 127.1 (CH), 127.3 (CH), 127.9 (CH), 128.4 (CH), 130.4 (CH), 137.7 (CCl), 141.8, 152.8 (C═O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −75.2 (d, *J* = 7.5 Hz); MS (ESI) calcd for $C_{17}H_{15}ClF_3N_2O$ (M + H) 355.0825, found 355.0821.

Compound 19 (Major Diastereomer). The enamine adduct was prepared following the general reaction procedure. A 50% excess of cyclopropyl methyl ketone pyrrolidine enamine was added to the mixture containing **11** at −60 °C. HPLC showed complete consumption of **11**. The reaction mixture was quenched by addition of 12% aqueous citric acid. The organic phase was washed with water and rotary evaporated at 28 °C. The residue was 89 area % adduct: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.04 (1H, m), 0.30 (1H, m), 0.59 (1H, m), 0.81 (2H, m), 1.65 (3H, d, *J* = 6.8 Hz), 1.92 (4H, m), 3.28 (4H, m), 4.28 (1H, s), 5.10 (1H, q, *J* = 6.8 Hz), 6.27 (1H, d, *J* = 8.4 Hz), 7.03 (1H, dd, *J* = 2.4 and 8.4 Hz), 7.19 (1H, m), 7.29 (2H, t, *J* = 7.5 Hz), 7.37 (1H, br s), 7.41 (2H, d, *J* = 7.5 Hz), 9.50 (1H, s, NH); ^{13}C NMR (75 MHz) δ 7.3 (CH_2), 8.0 (CH_2), 15.6 (CH), 20.2 (CH_3), 25.6 (CH_2 × 2), 48.9 (NCH_2 × 2), 56.1 (NCH), 70.6 (q, *J* = 26 Hz, NC), 88.9 (═CH), 115.4 (CH), 119.1 (C), 125.9 (CH), 126.0 (C), 126.4 (q, *J* = 290 Hz, CF_3), 126.6 (CH×2), 128.1 (CH×2), 129.7(CH), 130.5(CH), 136.2(C−Cl), 143.4 (C), 152.8 and 153.0 (C═O and N−C═); ^{19}F NMR (282 MHz) δ −79.0; MS (APcI) $(M + H)^+$, 490.

General Method for the Formic Acid Debenzylation.

DPC 961 (1): (4*S*)-6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,3,4-trihydroquinazolin-2-one (1). Compound **12** (25 kg, 59.6 mol) was stirred in 98% formic acid (150 kg) and heated to 60−65 °C for 1−3 h. The reaction was followed by HPLC and quenched when 1−4% of the starting material remained (extended heating causes solvolysis of the CPA group). Toluene (125 L) and water (125 L) were added to the reaction and the mixture cooled to 40−50 °C. The temperature was maintained above 40 °C to avoid premature crystallization. The layers were separated, and the toluene layer was washed with water (2× 125 L). The toluene phase was concentrated by atmospheric pressure distillation to 68 L, and heptanes (130 L) were added while 85−95 °C was maintained. The resulting slurry was cooled over 6 h to 0 °C. The crystals were filtered (the byproduct α-methylbenzyl formate remains in the liquors), washed with cold heptanes, and dried in a vacuum oven at 90 °C. The yield of **1** was 85% (16 kg), >96% pure and >98% ee

DPC 961 **1**. $[\alpha]^{25}_D$ −60 (*c* = 0.274, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72−0.87 (4H, m), 1.26 (1H, m), 6.78 (1H, d, *J* = 8.5 Hz), 6.80 (1H, s, NH), 7.23 (1H, dd, *J* = 8.5 Hz, *J* = 2.2 Hz), 7.49 (1H,s), 9.78 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.82 (CH), 8.49 (CH_2), 8.52 (CH_2), 59.1 (q, *J* = 33 Hz, C), 67.9 (C), 92.3 (C), 115.5 (C), 116.3 (CH), 123.6 (q, *J* = 288 Hz, C), 127.8 (C), 128.2 (CH), 130.9 (CH), 134.9 (CCl), 153.3 (C═O); ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.5.

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