Lithium Alkoxides of Cinchona Alkaloids as Chiral Controllers for Enantioselective Acetylide Addition to Cyclic *N*-Acyl Ketimines

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Highly enantioselective acetylide addition to cyclic *N*-acyl ketimines **1** can be carried out using the lithium alkoxide of quinine as a stoichiometric chiral additive. Quinidine can be used to give the opposite enantiomer. Optimization of temperature is critical, with low or high temperatures reducing selectivity. Using the bulky 9-anthrylmethyl protecting group at a distal position on the imine, a 97% ee was achieved and applied to the asymmetric synthesis of HIV reverse transcriptase inhibitor **3**.

Stereoselective methods for the addition of carbon nucleophiles to aldehydes and aldimines have been developed to synthesize nonracemic secondary carbinols and secondary carbinamines.[1] These types of targets can also be accessed by stereoselective reduction of ketones and ketimines.[2] However, the asymmetric synthesis of tertiary carbinols and carbinamines by addition of carbon nucleophiles to ketones and ketimines has enjoyed considerably less success.

Stereocontrolled additions to aldimines and their derivatives have employed chiral auxiliaries on the electrophile,[3] chiral auxiliaries on the nucleophile,[4] and noncovalently bound chiral additives.[5] Of these, the chiral additive method appears to be most advantageous because it avoids the auxiliary attachment and removal steps, and it holds the potential for direct recovery and reuse of the unchanged chiral reagent.

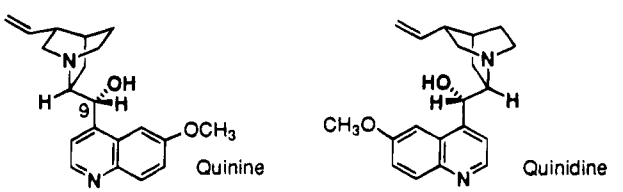
In seeking an efficient and scaleable route to the HIV reverse transcriptase inhibitor **3**, we faced the challenge of forming a tertiary carbinamine in an asymmetric manner. In the route to **3** via resolution,[6] this stereogenic center was formed by addition of an acetylide to cyclic *N*-acyl ketimine **1a** (Scheme 1). It appeared that the most efficient *asymmetric* route to **3** would involve carrying out this addition under the control of a chiral additive. Reported here is the development of a highly enantioselective (97% ee) acetylide addition using the lithium alkoxide of quinine as chiral controller.

Results and Discussion

A common type of chiral additive for organometallic additions to aldimines and aldehydes is a β-amino alcohol, deprotonated by the organometallic. In particular, a reagent of this type has been used for asymmetric acetylide addition to aldehydes.[7] While other types of chiral additives were screened for the present reaction (e.g. diamines, diethers), only β-amino alkoxides induced asymmetry.

For practical reasons, the search focused on readily available amino alcohols (Table 1). While ephedrine derivatives showed some selectivity, the most promising results were obtained with the cinchona alkaloids. Lithium alkoxides and acetylides (n-BuLi or $LiN(TMS)_2$ used to deprotonate the acetylene and the alcohol) gave better results than sodium ($NaN(TMS)_2$) or magnesium (EtMgBr) salts.[8] Homogeneous THF solutions of acetylide and alkoxide were more selective than the suspensions obtained with toluene or diethyl ether.

Quinine and dihydroquinine both favored the required (*S*)-enantiomer. Nearly equal selectivity for the other enantiomer is possible with quinidine. Small differences in magnitudes of selectivity may be in part due to alkaloid purity, since commercial samples of these natural products can be cross-contaminated with other members of the cinchona family. Because of the substantial advantage in cost and availability, we decided to optimize the use of quinine rather than dihydroquinine.



Since the protecting group on the distal nitrogen of **1** could be readily varied, electronic and steric effects were

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Scheme 1

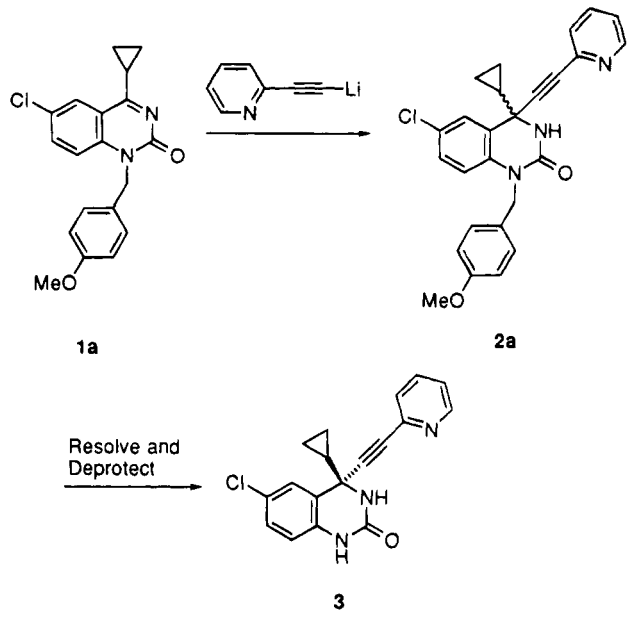
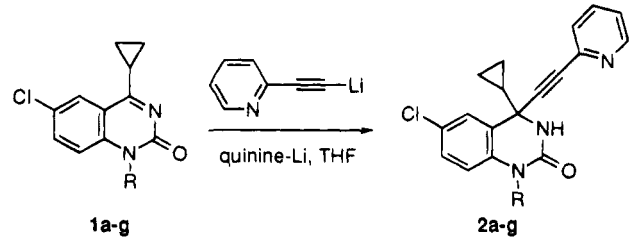


Table 1. Influence of β-Amino Alkoxides on Addition of 2-Ethynylpyridine to 1a

β-amino alcohol	ee (%)[a]	configuration
(1*R*,2*S*)-ephedrine	6	*S*
(1*R*,2*S*)-*N*-methylephedrine	10	*R*
(*S*)-1-methylpyrrolidine-2-methanol	0	
(*S*)-α,α-diphenylpyrrolidine-2-methanol	0	
quinine	59	*S*
dihydroquinine	64	*S*
cinchonidine	26	*S*
quinidine	55	*R*
dihydroquinidine	39	*R*
9-epiquinine	28	*S*

[a] 0.045 M **1a**, 0.068 M acetylide, 0.073 M alkoxide in THF at −45 to −20 °C with n-BuLi as base.

Table 2. Substituent Effects on Quinine-Mediated Addition of 2-Ethynylpyridine



1, 2	R	ee (%)[a]	best ee (%)[b]
a	4-methoxybenzyl	52	64
b	benzyl	53	56
c	4-chlorobenzyl	37	37
d	methyl	62	70[c]
e	2,4,6-trimethylbenzyl	60	74
f	2,6-dichlorobenzyl	69	80
g	9-anthrylmethyl	94	97

[a] Standardized conditions: 0.10 M **1**, 0.15 M acetylide, 0.16 M quinine alkoxide at −25 °C. [b] Best ee obtained; includes variations of temperature, concentration, solvent composition, and scale. [c] Dihydroquinine used in place of quinine.

probed for their effect on stereoselectivity (Table 2). As reactions with **1a−d** show, there is a substantial electronic influence with electron-withdrawing substituents decreasing enantioselectivity. Even more valuable and surprising is the effect of steric bulk at this remote position (**1e−g**). Large benzyl substituents provided substantial improvement, with excellent selectivity arising from the 9-anthrylmethyl group. It is not obvious why **1f** reacts more selectively than **1e**, especially in light of the expected negative effect of two electronegative chlorine substituents.

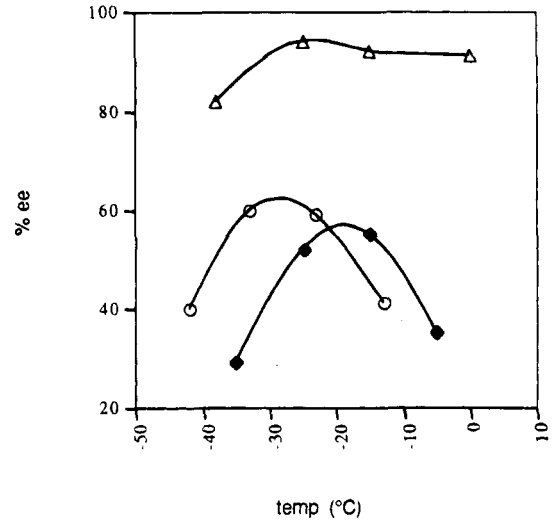


Figure 1. Temperature effect on enantioselectivity of quinine-mediated addition of 2-ethynylpyridine to **1a** (♦) and **1g** (△) (0.15 M acetylide, 0.16 M quinine alkoxide), and to **1e** (○) (0.11 M acetylide, 0.12 M quinine alkoxide).

In further optimizing selectivity, reaction temperature was varied, with dramatic results (Figure 1). With the 4-methoxybenzyl and 2,4,6-trimethylbenzyl-protected compounds **1a** and **1e**, an initial large *increase* in selectivity resulted from *increasing* temperature, with an equally steep decrease in selectivity above the optimum temperature. The same general behavior was seen with the 9-anthrylmethyl compound **1g**, although the curve is much shallower. This unusual behavior may reflect a temperature-dependent change in aggregation state of the lithium alkoxide and acetylide. Some interaction of the two species is apparent since the acetylide is only partially soluble in the absence of the alkoxide, but fully soluble in its presence. Nonetheless the same selectivity is observed whether the imine is added to a mixture of acetylide and alkoxide or the acetylide is added to a suspension of imine and alkoxide. Concentration also influences stereoselectivity, possibly by shifting the optimum temperature, but this factor was not systematically studied.

The 9-anthrylmethyl group has been reported as a protecting moiety for oxygen and sulfur.[9] It is also an effective nitrogen-protecting group, being readily cleaved with trifluoroacetic acid. The 2,4,6-trimethylbenzyl group is also cleaved under these conditions. However, the selectivity provided by the 9-anthrylmethyl group made it the protecting group of choice for the synthesis of **3** (Scheme 2). After protection of **4** with 9-(chloromethyl)-anthracene, acetylide addition was carried out at the optimum temperature of −25 °C giving a 97% ee for the reaction on large scale. Formation of the salt with (+)-camphorsulfonic acid provided a convenient isolation and allows for upgrade of the ee if necessary. Finally,

(8) There appears to be no precedent for the use of lithium alkoxides of the cinchona alkaloids in this way. Cinchona alkaloids have been used for asymmetric addition of diethylzinc to aldehydes, presumably involving zinc alkoxides: Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.

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Scheme 2

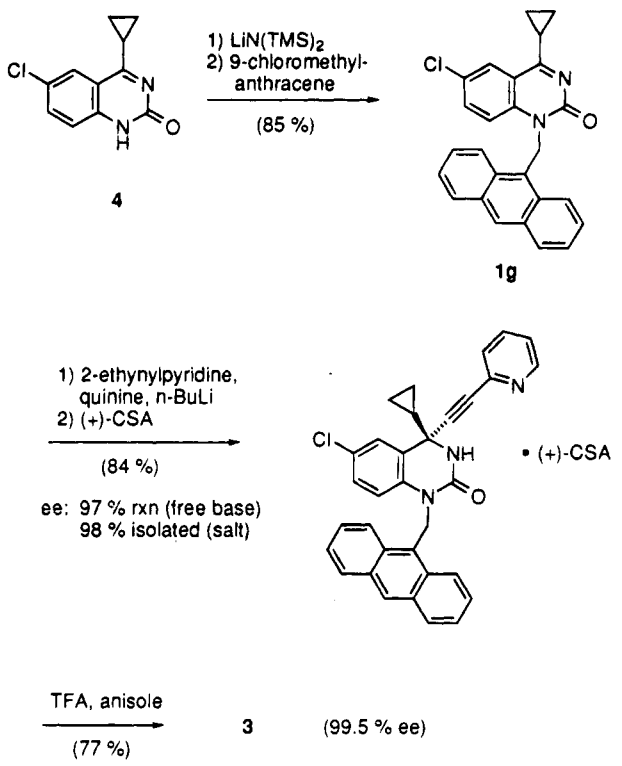
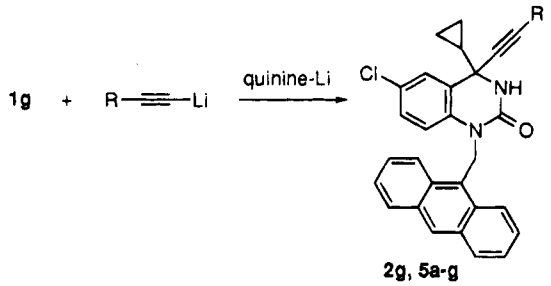


Table 3. Reaction of 1g with Acetylides in the Presence of Quinine Alkoxide



product	R	temp (°C)	ee (%)
2g	2-pyridyl[a]	−25	94
2g	2-pyridyl[a]	−15	92
5a	3-pyridyl[b]	−25	22
5a	3-pyridyl[b]	−15	36
5b	4-pyridyl[b]	−25	6
5b	4-pyridyl[b]	−15	13
5c	4-methoxyphenyl[b]	−15	86
5d	phenyl[b]	−15	65
5e	4-chlorophenyl[b]	−15	58
5f	butyl[b]	−25	77
5g	trimethylsilyl[b]	−25	82

[a] 0.10 M **1g**, 0.15 M acetylide, 0.16 M quinine alkoxide. [b] 0.050 M **1g**, 0.075 M acetylide, 0.080 M quinine alkoxide.

deprotection with trifluoroacetic acid and crystallization gave **3** in 99.5% ee.

In a brief exploration of the scope of this novel asymmetric reaction, other acetylides were reacted with **1g** (Table 3). Electron-rich aryl, alkyl, and silyl substituents gave good selectivity (**5c,f,g**), while more electron-deficient aryl acetylides were less selective (**5d,e**). No attempt was made to optimize these reactions. The 3- and 4-pyridyl acetylides reacted much less selectively than the 2-pyridyl case. However, comparison of the −25 °C and −15 °C reactions suggests that the optimum temperature for the 3- and 4-pyridyl cases may be somewhat higher. The high selectivity achieved with 2-pyridyl acetylide appears to lie outside the electronic trend, but the acute angle between the pyridine and C−Li dipoles may counteract the electron deficiency of the pyridine ring. As this angle increases, selectivity decreases (**5a,b**). The scope of the reaction regarding imine variation remains to be explored, but it is likely that extensive optimization including temperature and concentration will be required for each case.

Experimental Section

General. Amino alcohols were obtained from commercial sources except for (*S*)-pyrrolidine-2-diphenylmethanol[10] and 9-epiquinine[11] which were prepared according to literature procedures. Alkynes were purchased or prepared following published methods.[12] The preparations of 6-chloro-4-cyclopropylquinazolin-2(1*H*)-one (**4**) and 6-chloro-4-cyclopropyl-1-(4-methoxybenzyl)quinazolin-2(1*H*)-one (**1a**) have been reported previously.[6] THF and DMF were dried over 4A molecular sieves and residual water measured by Karl Fischer titration. All reactions were conducted under an atmosphere of dry N_2. Silica gel chromatography employed a column of Merck 230−400 mesh gel, eluting with ethyl acetate/hexanes mixtures. ^1H and ^{13}C NMR spectra were collected at 250 and 63 MHz, respectively, from samples in $CDCl_3$. FTIR spectra were obtained from CH_2Cl_2 solutions. Measurements of ee were conducted by chiral stationary phase HPLC, monitoring 254 nm with a flow rate of 1.0 mL/min. For **2a−g** and **5a,b** a Sumichiral OA 4700 4 × 250 mm column was used with a mobile phase of 3−4% EtOH and 0.2% TFA in hexanes. For **5c,g**, the mobile phase was 0.5% EtOH and 0.03% TFA, for **5d**, 1% EtOH and 0.05% TFA. For **5e** and **5f**, a YMC 3200 4 × 50 mm column was used with mobile phases of 1.25% EtOH and 0.6 % EtOH in hexanes respectively.

General Procedure for Addition of 2-Ethynylpyridine to 1a in the Presence of β-amino Alkoxides. A solution of 2-ethynylpyridine (76 μL, 0.75 mmol) and β-amino alcohol (0.80 mmol) in THF (10 mL, ≤25 μg water/mL) was cooled to −45 °C. A solution of n-BuLi in hexanes (1.0 mL of 1.6 M) was added slowly, maintaining internal temperature below −40 °C. After 60 min, **1a** was added as a solid and the suspension was allowed to warm slowly to −20 °C. When complete, the reaction was quenched with aqueous 1 N HCl and warmed to room temperature. After extraction with CH_2Cl_2/1 N HCl, the organic phase was dried over $MgSO_4$ and ee was measured on the crude product.

General Procedure for Protection of 4; Synthesis of 6-Chloro-4-cyclopropyl-1-(9-anthrylmethyl)quinazolin-2(1*H*)-one (1g). A 1 M solution of $LiN(TMS)_2$ in THF (4.28 mol) was slowly added to a suspension of **4** (785 g, 3.42 mol) in 16 L of THF and 2.3 L of DMF, maintaining temperature below 27 °C. NaI (743 g, 4.96 mol) and 9-(chloromethyl)-anthracene (965 g, 4.26 mol) were added, and the mixture was stirred at room temperature 24 h. After addition of 27 L of water, the mixture was filtered, washing the solid with water and methanol. The crude product was purified by slurrying in chlorobutane and filtering, and then slurrying in methanol and filtering. Vacuum drying gave 1214 g (85%) of **1g** of 98% purity. A small analytical sample of CH_2Cl_2 solvate was obtained by crystallization from CH_2Cl_2. **1g**: ^1H NMR δ 8.41 (m, 3H), 8.02 (d, J = 8.5 Hz, 2H), 7.91 (s, 1H), 7.61−7.45 (m, 4H), 7.02 (d, J = 1.5 Hz, 2H), 6.57 (s, 2H), 2.42 (m, 1H), 1.58 (m, 2H), 1.22 (m, 2H); ^{13}C NMR δ 177.9, 156.6, 140.6, 134.1, 131.3, 130.3, 129.7, 128.9, 127.6, 127.2, 127.1, 125.7, 125.1, 123.1, 118.4, 117.1, 42.1, 13.7, 12.9; IR 1654 (s). Anal. Calcd

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for $C_{27}H_{21}Cl_3N_2O$: C, 65.40; H, 4.27; N, 5.65. Found: C, 65.74; H, 4.17; N, 5.65.

6-Chloro-4-cyclopropyl-1-benzylquinazolin-2(1*H*)-one (1b). Alkylation of **4** (441 mg, 2.0 mmol) with benzyl bromide (310 μL, 2.6 mmol) in 8 mL of DMF gave, after silica gel chromatography, 480 mg (77%) of **1b**: ^{1}H NMR δ 8.10 (d, J = 2.2 Hz, 1H), 7.51 (dd, J = 9.1, 2.2 Hz, 1H), 7.32−7.14 (m, 6H), 5.46 (s, 2H), 2.52 (m, 1H), 1.56 (m, 2H), 1.25 (m, 2H); ^{13}C NMR δ 178.2, 155.8, 140.7, 135.5, 134.8, 128.9, 127.9, 127.6, 126.6, 126.1, 118.1, 116.6, 47.5, 13.8, 13.1; IR 1663 (s). Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01. Found: C, 69.34; H, 4.79; N, 8.89.

6-Chloro-4-cyclopropyl-1-(4-chlorobenzyl)quinazolin-2(1*H*)-one (1c). Alkylation of **4** (441 mg, 2.0 mmol) with 4-chlorobenzyl chloride (419 mg, 2.6 mmol) in 8 mL of DMF gave, after crystallization from methanol, 389 mg (56%) of **1c**: ^{1}H NMR δ 8.13 (d, J = 2.3 Hz, 1H), 7.55 (dd, J = 9.0, 2.3 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 9.0 Hz, 1H), 5.43 (s, 2H), 2.54 (m, 1H), 1.57 (m, 2H), 1.26 (m, 2H); ^{13}C NMR δ 178.4, 155.6, 140.4, 134.9, 134.0, 133.5, 129.1, 128.1, 126.2, 118.1, 116.3, 46.9, 13.8, 13.2; IR 1658 (s). Anal. Calcd for $C_{18}H_{14}Cl_2N_2O$: C, 62.62; H, 4.09; N, 8.11. Found: C, 62.37; H, 3.94; N, 7.93.

6-Chloro-4-cyclopropyl-1-methylquinazolin-2(1*H*)-one (1d). Alkylation of **4** (441 mg, 2.0 mmol) with MeI (190 μL, 3.0 mmol) in 8 mL of DMF without NaI gave, after crystallization from diethyl ether, 317 mg (66%) of **1d**: ^{1}H NMR δ 8.01 (d, J = 2.3 Hz, 1H), 7.70 (dd, J = 9.0, 2.3 Hz, 1H), 7.26 (d, J = 9.0 Hz, 1H), 3.67 (s, 3H), 2.47 (m, 1H), 1.49 (m, 2H), 1.21 (m, 2H); ^{13}C NMR δ 177.6, 155.6, 141.3, 134.9, 127.8, 126.0, 117.8, 115.7, 31.0, 13.6, 12.9; IR 1656 (s). Anal. Calcd for $C_{12}H_{11}ClN_2O$: C, 61.42; H, 4.72; N, 11.94. Found: C, 61.23; H, 4.58; N, 11.78.

6-Chloro-4-cyclopropyl-1-(2,4,6-trimethylbenzyl)-quinazolin-2(1*H*)-one (1e). Alkylation of **4** (441 mg, 2.0 mmol) with 2,4,6-trimethylbenzyl chloride (405 mg, 2.4 mmol) gave, after silica gel chromatography, 551 mg (78%) of **1e**: ^{1}H NMR δ 8.06 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 9.1, 2.4 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 6.79 (s, 2H), 5.55 (s, 2H), 2.50 (m, 1H), 2.22 (s, 3H), 2.19 (s, 6H), 1.53 (m, 2H), 1.22 (m, 2H); ^{13}C NMR δ 177.7, 156.0, 140.5, 136.9, 135.9, 134.5, 130.2, 129.6, 127.7, 125.8, 118.1, 116.5, 44.0, 20.7, 20.2, 13.6, 12.8; IR 1654 (s). Anal. Calcd for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94. Found: C, 71.08; H, 5.96; N, 7.61.

6-Chloro-4-cyclopropyl-1-(2,6-dichlorobenzyl)quinazolin-2(1*H*)-one (1f). Alkylation of **4** (3.00 g, 13.6 mmol) with 2,6-dichlorobenzyl bromide (4.08 g, 17.0 mmol) gave, after consecutive crystallizations from ethyl acetate/hexanes and from methanol, 3.12 g (60%) of **1f**: ^{1}H NMR δ 8.08 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 8.9, 2.3 Hz, 1H), 7.29 (m, 2H), 7.16 (dd, J = 9.0, 7.0 Hz, 1H), 7.07 (d, J = 9.1 Hz, 1H), 5.82 (s, 2H), 2.50 (m, 1H), 1.54 (m, 2H), 1.23, (m, 2H); ^{13}C NMR δ 178.0, 156.0, 140.2, 135.4, 134.6, 130.9, 129.5, 129.3, 127.8, 126.2, 118.3, 116.2, 43.8, 13.8, 12.9; IR 1664 (s). Anal. Calcd for $C_{18}H_{13}Cl3N_2O$: C, 56.94; H, 3.45; N, 7.38. Found: C, 56.68; H, 3.30; N, 7.26.

General Procedure for Addition of Acetylides to 1 in the Presence of Quinine Alkoxide. A solution of alkyne (0.75 mmol) and quinine (260 mg, 0.80 mmol) in THF (4 mL or 9 mL, ≤25 μg of water/mL) was cooled to −45 to −50 °C and treated with n-BuLi (1.0 mL of 1.6 M in hexanes) maintaining temperature below −40 °C. The solution was then warmed to the specified temperature and **1** was added as a solid. When complete, the reaction was quenched with aqueous 1 N HCl and warmed to room temperature. After partitioning between CH_2Cl_2 and aqueous 1 N HCl, the organic phase was dried over $MgSO_4$ and evaporated. Measurement of ee was carried out on the crude solids.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(4-methoxybenzyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2a). In 4 mL of THF, ee was 29% at −35 °C, 52% at −25 °C, 55% at −15 °C, 35% at −5 °C. In 5 mL of THF and 4 mL of hexanes, over −45 to −20 °C, 64% ee. Crystallization from methanol gave 189 mg (85%). Spectral data matched those previously reported.[6]

6-Chloro-4-cyclopropyl-3,4-dihydro-1-benzyl-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2b). In 4 mL of THF at −25 °C, 53% ee. In 10 mL of THF over −45 to −25 °C, 56% ee. Silica gel chromatography gave 154 mg (74%). ^{1}H NMR δ 8.59 (dm, J = 5.0 Hz, 1H), 7.64 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.38 (dm, J = 7.8 Hz, 1H), 7.36−7.20 (m, 6H), 7.11 (dd, J = 8.8, 2.5 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.5 (s, 1H), 5.30 (d, J = 16.7 Hz, 1H), 5.11 (d, J = 16.7 Hz, 1H), 1.56 (m, 1H), 1.04 (m, 1H), 0.90 (m, 1H), 0.81 (m, 1H), 0.72 (m, 1H); ^{13}C NMR δ 153.9, 150.1, 142.1, 136.6, 136.1, 135.5, 128.9, 128.8, 127.9, 127.6, 127.2, 127.1, 126.3, 125.5, 123.4, 115.9, 85.6, 56.8, 46.0, 21.0, 3.7, 0.7; IR 3406, 1683 (s). Anal. Calcd for $C_{25}H_{20}ClN_3O$: C, 72.55; H, 4.87; N, 10.15. Found: C, 72.27; H, 4.81; N, 10.01.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(4-chlorobenzyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2c). In 4 mL of THF at −25 °C, 37% ee. Silica gel chromatography gave 181 mg (80%). ^{1}H NMR of 8.59 (dm, J = 4.7 Hz, 1H), 7.65 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.35 (dm, J = 7.8 Hz, 1H), 7.29−7.16 (m, 5H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 5.30 (d, J = 16.8 Hz, 1H), 5.06 (d, J = 16.8 Hz, 1H), 1.55 (m, 1H), 1.02 (m, 1H), 0.92 (m, 1H), 0.81 (m, 1H), 0.69 (m, 1H); ^{13}C NMR δ 153.9, 150.1, 142.0, 136.1, 135.3, 135.2, 132.9, 128.9, 128.1, 127.9, 127.5, 127.3, 125.6, 123.4, 115.7, 85.7, 85.5, 56.7, 45.4, 20.8, 3.7, 0.7; IR 3407, 1684 (s). Anal. Calcd for $C_{25}H_{19}Cl_2N_3O$: C, 66.97; H, 4.27; N, 9.37. Found: C, 66.62; H, 4.24; N, 9.17.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-methyl-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2d). In 4 mL of THF at −25 °C, 62% ee. Using dihydroquinine in 10 mL of THF over −50 to −20 °C, 70% ee. Silica gel chromatography gave 130 mg (77%). ^{1}H NMR δ 8.55 (brd, J = 4.4 Hz, 1H), 7.63 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 8.7, 2.4 Hz, 1H), 7.23 (m, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.48 (s, 1H), 3.35 (s, 3H), 1.51 (m, 1H), 1.48 (m, 1H), 0.88−0.62 (m, 3H); ^{13}C NMR δ 153.4, 149.9, 142.0, 136.5, 136.0, 128.8, 127.6, 127.5, 126.5, 125.5, 123.2, 114.6, 85.6, 85.1, 56.5, 29.7, 21.3, 3.5, 0.7; IR 3410, 1683 (s). Anal. Calcd for $C_{19}H_{16}ClN_3O$: C, 67.56; H, 4.77; N, 12.44. Found: C, 67.19; H, 4.75; N, 12.23.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(2,4,6-trimethylbenzyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2e). In 4 mL of THF at −25 °C, 60% ee. In 10 mL of THF over −45 to −20 °C, 74% ee. In 4 mL of THF using 0.50 mmol of alkyne and 0.53 mmol quinine, ee was 40% at −42 °C, 60% at −33 °C, 59% at −23 °C, 41% at −13 °C. Silica gel chromatography gave 182 mg (80%). ^{1}H NMR δ 8.56 (brd, J = 4.7 Hz), 7.62 (ddd, J = 7.7, 1.7, 1.7 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.22 (m, 1H), 7.08 (dd, J = 8.8, 2.5 Hz, 1H), 6.75 (s, 2H), 6.66 (d, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.47 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 16.0 Hz, 1H), 2.36 (s, 6H), 2.20 (s, 3H), 1.50 (m, 1H), 1.06 (m, 1H), 0.90 (m, 1H), 0.78 (m, 1H), 0.65 (m, 1H); ^{13}C NMR δ 153.8, 150.0, 142.1, 136.6, 136.5, 136.1, 135.7, 129.9, 129.8, 128.8, 127.7, 127.4, 127.1, 125.7, 123.3, 115.6, 86.4, 85.6, 56.3, 42.2, 21.5, 20.7, 20.5, 4.0, 0.6; IR 3410, 1676 (s). Anal. Calcd for $C_{28}H_{26}ClN_3O$: C, 73.75; H, 5.75; N, 9.22. Found: C, 73.39; H, 5.68; N, 9.10.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(2,6-dichlorobenzyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2f). In 4 mL of THF at −25 °C, 69% ee. In 10 mL of THF at −25 °C, 80% ee. Silica gel chromatography gave 183 mg (76%). ^{1}H NMR δ 8.58 (dm, J = 4.7 Hz, 1H), 7.65 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.38 (dm, J = 7.8 Hz, 1H), 7.28−7.08 (m, 5H), 6.95 (d, J = 8.8 Hz, 1H), 5.60 (d, J = 15.9 Hz, 1H), 5.53 (s, 1H), 5.37 (d, J = 15.9 Hz, 1H), 1.57 (m, 1H), 1.02 (m, 1H), 0.82 (m, 2H), 0.66 (m, 1H); ^{13}C NMR δ 153.4, 150.0, 142.2, 136.0, 135.9, 135.0, 131.6, 129.2, 129.0, 128.7, 127.8, 127.6, 127.5, 125.9, 123.3, 115.5, 85.7, 85.6, 56.8, 41.8, 21.9, 3.9, 0.9; IR 3413, 1685 (s). Anal. Calcd for $C_{25}H_{18}Cl_3N_3O$: C, 62.19; H, 3.76; N, 8.70. Found: C, 61.87; H, 3.70; N, 8.61.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (2g). In 4 mL of THF, ee was 82% at −38 °C, 94% at −25 °C, 92% at −15 °C, 91% at 0 °C. Crystallization from MeOH gave 229

mg (89%). ^{1}H NMR δ 8.57 (dm, J = 4.6 Hz, 1H), 8.46 (d, J = 8.8 Hz, 2H), 8.38 (s, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.57 (ddd, J = 7.2, 7.2, 1.8 Hz, 1H), 7.45 (m, 2H), 7.40 (d, J = 2.3 Hz, 1H), 7.34–7.22 (m, 3H), 7.04 (dm, J = 7.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8, 2.3 Hz, 1H), 6.28 (d, J = 15.9 Hz, 1H), 6.16 (d, J = 15.9 Hz, 1H), 5.71 (s, 1H), 1.37 (m, 1H), 0.77 (m, 2H), 0.60 (m, 2H); ^{13}C NMR δ 154.4, 149.9, 142.0, 136.0, 135.2, 131.3, 130.6, 129.4, 128.5, 128.3, 127.8, 127.7, 127.6, 127.3, 126.5, 125.4, 124.8, 123.7, 123.3, 116.5, 85.5, 85.0, 56.8, 39.5, 21.3, 3.7, 1.0; IR 3408, 1674 (s). Anal. Calcd for $C_{33}H_{24}ClN_3O$: C, 77.11; H, 4.71; N, 8.17. Found: C, 76.80; H,4.61; N, 8.09.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(3-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (5a). In 10 mL of THF, 22% ee at −25 °C, 36% ee at −15 °C. Crystallization from methanol gave 177 mg (69%). ^{1}H NMR δ 8.53 (dd, J = 4.9, 1.7 Hz, 1H), 8.45 (d, J = 8.9 Hz, 2H), 8.38 (s, 1H), 8.32 (brd, J = 1.5 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.42 (m, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.31 (m, 3H), 7.17 (brdd, J = 7.8, 4.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 6.38 (d, J = 15.8 Hz, 1H), 6.04 (d, J = 15.8 Hz, 1H), 5.71 (s, 1H), 1.37 (m, 1H), 0.71 (m, 4H); ^{13}C NMR δ 154.6, 152.3, 149.0, 138.9, 135.3, 131.3, 130.6, 129.5, 128.6, 128.4, 128.1, 127.6, 127.4, 126.5, 125.1, 124.8, 123.7, 122.8, 118.8, 116.6, 88.9, 82.8, 56.6, 39.4, 20.8, 3.7, 0.7; IR 3410, 1674 (s). Anal. Calcd for $C_{33}H_{24}ClN_3O$: C, 77.11; H, 4.71; N, 8.17. Found: C, 76.18; H, 4.68; N, 8.00.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(4-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (5b). In 10 mL of THF, 6% ee at −25 °C, 13% ee at −15 °C. Silica gel chromatography and crystallization from methanol gave 155 mg (60%). ^{1}H NMR δ 8.54 (brs, 1H), 8.46 (d, J = 8.8 Hz, 2H), 8.41 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.43 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.32 (m, 3H), 6.99 (d, J = 8.8 Hz, 1H), 6.92 (brs, 2H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 6.02 (d, J = 15.8 Hz, 1H), 5.70 (s, 1H), 1.41 (m, 1H), 0.70 (m, 4H); ^{13}C NMR δ 154.6, 149.5, 135.4, 131.3, 130.6, 129.8, 129.5, 128.6, 128.5, 127.8, 127.7, 127.3, 126.5, 125.1, 124.9, 123.7, 116.6, 90.2, 83.5, 56.5, 39.4, 20.6, 3.7, 0.7; IR 3408, 1675 (s). Anal. Calcd for $C_{33}H_{24}ClN_3O$: C, 77.11; H, 4.71; N, 8.17. Found: C, 76.33; H, 4.64; N, 8.00.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(4-methoxyphenyl)ethyn-1-yl]quinazolin-2(1*H*)-one (5c). In 10 mL of THF at −15 °C, 86% ee. Silica gel chromatography gave 221 mg (81%). ^{1}H NMR δ 8.48 (d, J = 8.9 Hz, 2H), 8.40 (s, 1H), 7.98 (d, J = 7.8 Hz, 2H), 7.46 (m, 2H), 7.37 (m, 2H), 7.35 (d, J = 2.4 Hz, 1H), 7.13 (dm, J = 8.9 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.80 (dm, J = 8,9 Hz, 2H), 6.78 (dd, J = 8.8, 2.4 Hz, 1H), 6.24 (s, 2H), 5.60 (s, 1H), 3.83 (s, 3H), 1.32 (m, 1H), 0.71 (m, 2H), 0.55 (m, 2H); ^{13}C NMR δ 160.0, 154.6, 135.1, 133.4, 131.3, 130.6, 129.5, 128.6, 128.5, 128.1, 127.4, 126.6, 125.3, 124.9, 123.7, 116.5, 113.8, 113.7, 86.3, 83.8, 57.1, 55.3, 39.4, 21.5, 3.6, 1.0; IR 3413, 1674 (s), 1511 (s). Anal. Calcd for $C_{33}H_{24}ClN_2O_2$: C, 77.41; H, 5.01; N, 5.06. Found: C, 76.78; H, 4.88; N, 5.01.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-(2-phenylethyn-1-yl)quinazolin-2(1*H*)-one (5d). In 10 mL of THF at −15 °C, 65% ee. Silica gel chromatography and crystallization from methanol gave 160 mg (62%). ^{1}H NMR δ 8.48 (d, J = 9.1 Hz, 2H), 8.40 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.49–7.17 (m, 10 H), 6.91 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 6.20 (d, J = 16.0 Hz, 1H), 5.61 (s, 1H), 1.34 (m, 1H), 0.73 (m, 2H), 0.58 (m, 2H); ^{13}C NMR δ 154.6, 135.1, 132.0, 131.4, 130.6, 129.5, 128.8, 128.5, 128.4, 128.2, 128.1, 127.5, 127.4, 126.6, 125.3, 124.9, 123.7, 121.6, 116.5, 86.3, 85.2, 57.0, 39.5, 21.4, 3.6, 1.0; IR 3409, 1673 (s). Anal. Calcd for $C_{34}H_{25}ClN_2O$: C, 79.50; H, 4.81; N, 5.46. Found: C, 79.41; H, 4.84; N, 5.33.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(4-chlorophenyl)ethyn-1-yl]quinazolin-2(1*H*)-one (5e). In 10 mL of THF at −15 °C, 58% ee. Silica gel chromatography gave 225 mg (82%). ^{1}H NMR δ 8.47 (d, J = 8.8 Hz, 2H), 8.40 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.48–7.32 (m, 5H), 7.24 (dm, J = 8.5 Hz, 2H), 7.04 (dm, J = 8.5 Hz, 2H), 6.94 (d, J = 8.8 Hz, 1H), 6.82 (dd, J = 8.8, 2.5 Hz, 1H), 6.34 (d, J = 15.9 Hz, 1H), 6.12 (d, J = 15.9 Hz, 1H), 5.62 (s, 1H), 1.36 (m, 1H), 0.72–0.60 (m, 4H); ^{13}C NMR δ 154.6, 135.2, 134.8, 133.2, 131.4, 130.6, 129.5, 128.6, 128.5, 128.2, 127.5, 127.4, 126.5, 125.2, 124.9, 123.7, 120.1, 116.5, 86.4, 85.1, 56.8, 39.5, 21.1, 3.6, 0.8; IR 3410, 1673 (s). Anal. Calcd for $C_{34}H_{24}Cl_2N_2O$: C, 74.59; H, 4.42; N, 5.12. Found: C, 74.34; H, 4.39; N, 5.06.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-(hexyn-1-yl)quinazolin-2(1*H*)-one (5f). In 10 mL of THF at −25 °C, 77% ee. Crystallization from methanol gave 187 mg (76%). ^{1}H NMR δ 8.48 (d, J = 8.9 Hz, 2H), 8.40 (s, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.58–7.42 (m, 4H), 7.26 (d, J = 2.6 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.6 Hz, 1H), 6.31 (d, J = 15.9 Hz, 1H), 6.11 (d, J = 15.9 Hz, 1H), 5.45 (s, 1H), 2.03 (m, 2H), 1.35 (m, 4H), 1.18 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H), 0.61–0.40 (m, 4H); ^{13}C NMR δ 154.6, 134.9, 131.4, 130.6, 129.5, 129.1, 128.5, 127.9, 127.6, 127.4, 126.4, 125.3, 124.9, 123.9, 116.3, 87.4, 76.1, 56.9, 39.3, 30.5, 22.0, 21.3, 18.2, 13.5, 3.4, 1.0; IR 3415, 1672 (s). Anal. Calcd for $C_{32}H_{29}ClN_2O$: C, 77.95; H, 5.93; N, 5.68. Found: C, 77.66; H, 5.82; N, 5.64.

6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(trimethylsilyl)ethyn-1-yl]quinazolin-2(1*H*)-one (5g). In 10 mL of THF at −25 °C, 82% ee. Workup with water in place of 1 N HCl, followed by crystallization from methanol, gave 197 mg (77) %. ^{1}H NMR δ 8.46 (d, J = 8.9 Hz, 2H), 8.40 (s, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.59–7.42 (m, 4H), 7.23 (d, J = 2.3 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.8, 2.3 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 5.98 (d, J = 16.0 Hz, 1H), 5.48 (s, 1H), 1.17 (m, 1H), 0.62–0.45 (m, 2H), 0.35 (m, 1H), 0.15 (s, 9H); ^{13}C NMR δ 154.2, 134.8, 131.4, 130.6, 129.6, 128.5, 128.1, 127.8, 127.5, 127.4, 126.5, 125.6, 124.9, 123.8, 116.4, 100.8, 91.6, 57.6, 39.4, 21.9, 3.5. 1.3, −0.2; IR 3415, 1673 (s). Anal. Calcd for $C_{31}H_{29}ClN_2OSi$: C, 73.13; H, 5.74; N, 5.50. Found: C, 72.79; H, 5.54; N, 5.46.

Preparation of 6-Chloro-4-cyclopropyl-3,4-dihydro-1-(9-anthrylmethyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one−(+)-Camphorsulfonic acid [2g·(+)-CSA]. A solution of 2-ethynylpyridine (372 mL, 3.68 mol) and quinine (1278 g, 3.94 mol) in THF (21 L, 23 μg of water/mL) was cooled to −52 °C. n-BuLi in hexanes (7.83 mol of 1.72 M) was added slowly, maintaining temperature below −37 °C. The solution was then allowed to warm to −25 °C, and solid **1g** (1080 g of 98 wt % purity, 2.58 mol) was added. After 14 h, the mixture was quenched with 10 L of 10% H_2SO_4 followed by 10 L of saturated aqueous NaCl. After phase separation, the organic layer was dried over $MgSO_4$ and concentrated to 15 L. Crude product ee was 97%. Addition of (+)-CSA produced crystals which were collected and rinsed with THF, giving 1823 g (2.16 mol, 84%) of a THF solvate of **2g**·(+)-CSA. A small sample was dissolved in CH_2Cl_2 and washed with aqueous NaOH. The ee of free **2g** was 98%.

Preparation of (S)-(−)-6-Chloro-4-cyclopropyl-3,4-dihydro-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (3). Solid **2g**·(+)-CSA THF solvate (1700 g, 2.01 mol) was added in portions to a mixture of anisole (1.8 L) and TFA (2.0 L), keeping the temperature below 25 °C. After 23 h at room temperature, the mixture was concentrated, redissolved in a mixture of ethyl acetate and saturated aqueous NaCl, and neutralized with NaOH. The organic layer was separated, and the ethyl acetate was replaced with methanol/water by vacuum distillation. The mixture was filtered and the filtrate was purified by chromatography on a Mitsubishi Kasei SP 206 resin (17 L), eluting with 98% methanol/water. Evaporation and crystallization from ethyl acetate gave **3** as an ethyl acetate solvate. Distilling ethyl acetate from a suspension in water at 100 °C, followed by cooling and filtration gave **3** monohydrate (532 g, 77%) which was identical to material previously reported.[6]

Supplementary Material Available: Copies of ^{1}H NMR spectra of **5a–c** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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