N–C Axially Chiral Compounds with an ortho -Fluoro Substituent and Steric Discrimination between Hydrogen and Fluorine Atoms Based on a Diastereoselective Model Reaction

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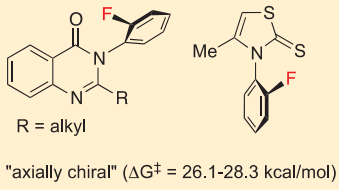
ABSTRACT: The fluorine atom is the second smallest atom; nevertheless, the *ortho*-fluoro group may lead to stable *N*-aryl atropisomers when the steric demand of the flanking substituents is large enough. 2-Alkyl-3-(2-fluorophenyl)quinazolin-4-ones and 3-(2-fluorophenyl)-4-methylthiazoline-2-thione were found to be the first *N*-aryl axially chiral compounds bearing an *ortho*-fluoro group whose enantiomers were isolated at ambient temperature. The reaction of alkyl halides with the anionic species prepared from 2-ethyl-3-(2-fluorophenyl)quinazolin-4-one presenting an N–C axial chirality provided a model reaction for quantitative evaluation of the steric discrimination (slight difference of steric factor) between hydrogen and fluorine atoms. In the case of low steric demand (allylation reaction) no diastereoselectivity was detected, while in the case of high steric demand (isopropylation reaction) the diastereoselectivity became significant.



INTRODUCTION

Recently, chiral molecules due to the rotational restriction around an N–Ar bond have attracted considerable attention as a new class of nonbiaryl atropisomeric compound.[1] Most of these chiral molecules have an ortho-substituted aniline skeleton, and the rotational stability around an N–Ar axis is significantly influenced by the structure on the nitrogen side as well as the steric factor of an ortho substituent on the Ar group. For example, in anilide derivatives, a bulky ortho substituent such as a *tert*-butyl group is required for a rotationally stable structure,[2] while among 3-arylthiazoline-2-thiones (Figure 1, **I**) and 3-arylquinazolin-4-ones (Figure 1, **II**), compounds **IB**, **IC**, **IIB**, and **IIC** bearing relatively small ortho substituents such as Cl and Me groups possess a stable atropisomeric structure.[3,4]

On the other hand, the N–C axially chiral compounds bearing an *ortho*-fluoro group have to date remained uncommon because the steric size of a fluorine atom is supposedly too small to restrict the rotation around the N–Ar bond. Indeed, in 3-arylthiazoline-2-thione **I**, the rotational barrier of **IA** (X = F) is significantly lower (12.2 kcal/mol) than that of **IB** (X = Cl).[3c] Also, among 3-arylquinazolin-4-one derivatives, it has been reported that the compound shown in Figure 1, **IIIA** (a smooth muscle contractile agent), with its *ortho*-fluorophenyl group is rotationally unstable, and its enantiomers could not be isolated at ambient temperature.[5] Furthermore, although the antiviral quinazolinone shown in Figure 1, **IVA**, is also well known, there is no report of its N–C axial chirality.[6] To the best of our knowledge, the known *ortho*-fluoro-aniline derivatives with the highest rotational barrier are pyrimidine-2,4-dione **VA** and quinolin-2-one **VIA** (Figure 1). The rotational barriers of **VA** and **VIA** are 25.1 kcal/mol; such barriers are high enough to allow a baseline separation without interconversion of the enantiomers on the column; however, collection and storage of the enantiomers require special care to prevent racemization ($t_{1/2}$ = 1.4 days at 298 K).[7,8]

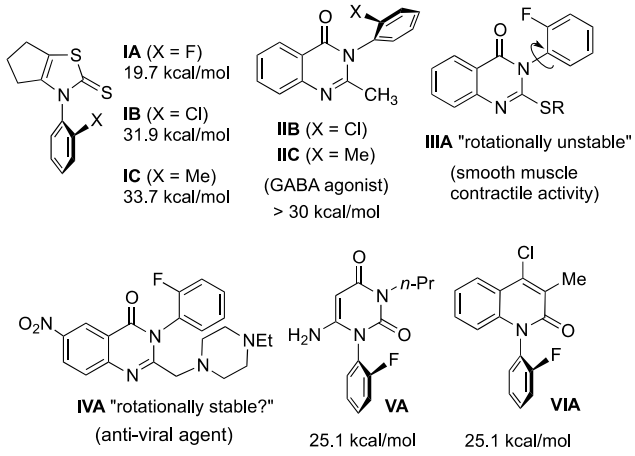
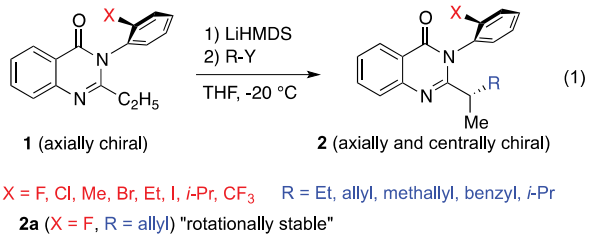


Figure 1. Various N–C axially chiral compounds and their rotational barriers.

As shown in eq 1, we recently reported the α-alkylation of anionic species prepared from N−C axially chiral 2-ethyl-

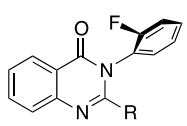


quinazolin-4-ones bearing various ortho-substituted phenyl groups on the nitrogen atom.[9] The reaction proceeded with stereocontrol due to axial chirality to preferentially afford the products **2** with a (*P, S*)-configuration.

In the course of this work, it was found that no N−C bond rotation occurs in the diastereomeric allylation product **2a** (X = F, R = allyl) bearing an *ortho*-fluorophenyl group even after standing for 24 h at rt in THF (eq 1).[9b] The unexpected rotational stability of **2a** aroused our interest for the atropisomerism resulting from fluorine as a blocking substituent and for experimental evidence of the steric discrimination between the two smallest substituents: fluorine and hydrogen. In this article, we discuss several rare N−C axially chiral compounds (3-arylquinazolin-4-ones and 3-arylthiazoline-2-thiones) bearing a *N-ortho*-fluorophenyl group. We also describe the reaction of alkyl halides with the anionic species prepared from 2-ethyl-3-(2-fluorophenyl)-quinazolin-4-one with stereocontrol based on the discrimination between *ortho*-hydrogen and *ortho*-fluorine atoms.

RESULTS AND DISCUSSION

Initially we thought that the rotational stability of **2a**, which differs from that of **IIIA**, may be due to the bulky alkyl group at C2. To verify the substituent effect at C2, 3-(2-fluorophenyl)-quinazolin-4-ones **1a−c** bearing three C2-alkyl groups (Me, Et, *i*-Pr) were prepared by cyclocondensation of the corresponding *N*-acylanthranilic acid with 2-fluoroaniline, followed by HPLC enantiomer separation using a Chiralpak AS-H column. Subsequently, the rate constants for the racemization of the obtained optically pure **1a−c** were measured at three different temperatures in CCl_4, and these data were subjected to an Eyring plot to determine the rotational barriers (Figure 2 and see SI).



	$\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$ (days)
1a (R = Et)	26.5	17.0
1b (R = Me)	26.1	8.7
1c (R = *i*-Pr)	26.2	10.4

Figure 2. Rotational barriers and half-life time of quinazolinones **1a−c** at 25 °C in CCl_4.

The rotational barrier and half-life time for the racemization of the 2-ethyl derivative **1a** at 298 K in CCl_4 were evaluated to be 26.5 kcal/mol and 17 days, demonstrating sufficient stability for a convenient isolation of the enantiomers. For the 2-methyl and 2-isopropyl derivatives **1b** and **1c**, although a slight decrease in the rotational barriers was observed (26.1 and 26.2 kcal/mol), rotational stability at ambient temperature was maintained ($t_{1/2}$ of **1b** and **1c** at 25 °C = 8.7 and 10.4 days). These results indicate that the rotational barriers in quinazolinone derivatives bearing an *ortho*-fluorophenyl group are not remarkably affected by the steric effect of the C2-alkyl group in the series Me, Et, *i*-Pr.

The rotational instability of **IIIA**, which markedly differs from the high rotational stability in **1a−c**, may be explained with reference to Figure 3. We previously reported that the N−

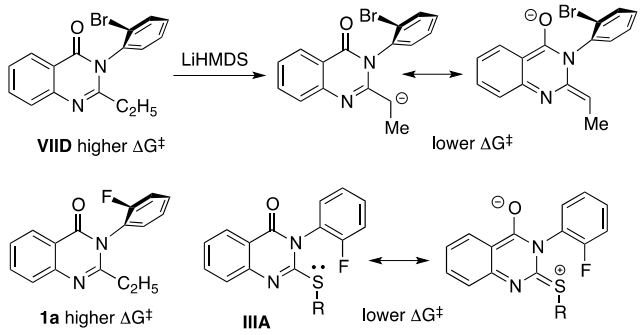


Figure 3. Relationship between nearby structures and the rotational barrier around an N−C bond.

C bond rotation of the anionic species prepared from quinazolinone **VIID** with an *ortho*-bromophenyl group occurs easily at ambient temperature, in remarkable contrast with neutral **VIID**, which presents a high rotational barrier (ca. $\Delta G^{\ddagger}$ = 35 kcal/mol).[9a] The structure of quinazolinone **IIIA** with an alkylthio group at C2 may be similar to the anionic species of **VIID** because of the positive resonance effect involving the lone electron pair on sulfur. The electron-donating effect of the sulfur atom in **IIIA** would be weak in comparison with that in the anionic intermediate **VIID**. Meanwhile, since the rotational barriers of quinazolinones bearing an *ortho*-fluorophenyl group are not so high (ca. $\Delta G^{\ddagger}$ = 26 kcal/mol), the slight decrease in the barrier caused by the weak electron-donating character of sulfur atom may result in the difficulty of the enantiomer separation in **VIID**. In addition, a possible attractive electrostatic interaction between the electron-rich fluorine atom and the positively charged sulfur atom in the near planar transition state of the N−C bond rotation may account for the relative rotational instability in **IIIA**.

Although the rotationally stable quinazolinone derivatives **1a−c** bearing an *ortho*-fluorophenyl group were found unexpectedly,[10] we designed other N−C axially chiral compounds [*N*-(*ortho*-fluorophenyl)thiazoline-2-thione derivatives **3**] to have a higher rotational barrier than **1a−c**. As mentioned above, cyclopentane-fused thiazoline-2-thione **IA** is rotationally unstable at ambient temperature ($\Delta G^{\ddagger}$ = 19.7 kcal/mol, Figures 1 and 4).[3c] In order to increase the rotational barrier by structural modification, we envisioned the

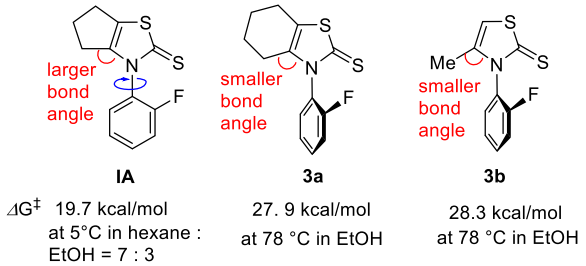


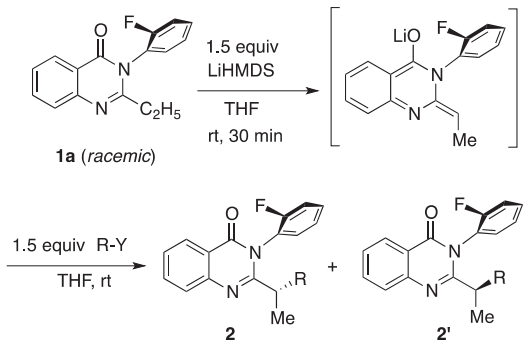
Figure 4. Rotational barriers in *N*-(2-fluorophenyl)thiazoline-2-thione derivatives.

introduction of different groups on position 4 of the heterocyclic moiety. Indeed, previously described X-ray crystal analyses of *N*-aryl-thiazoline-2-thiones showed unambiguously that the resulting rotational barriers in these series were directly related to the angle between the endocyclic nitrogen atom and the substituent on position 4 of the thiazoline ring.[11] For instance, this angle, which is crucial for enantiomeric stability, was found to be 120−121° for 4-methyl thiazoline-2-thiones,[11] compared to the 131° found for the five-membered ring analogues,[3c] making the rotation about the pivotal bond more difficult in the first case. Thus, the targeted cyclohexane-fused and 4-methylated *N*-(*ortho*-fluorophenyl)-thiazoline-2-thiones **3a** and **3b** (Figure 4) were synthesized by treatment of *ortho*-fluoroaniline with carbon disulfide to generate the dithiocarbamate salt, which was allowed to react with 2-chlorocyclohexanone or 2-chloroacetone, respectively (see SI).[11]

Enantiomers were easily obtained by preparative HPLC on the chiral support of an (*S*,*S*) Whelk-O1 column, and kinetic studies of the thermal racemization of the atropisomers permitted measurement of the rotational barriers at a specified temperature. As expected, these structural modifications notably increased the rotational barriers. For compound **3a**, a $\Delta G^{\ddagger}$ value of 27.9 kcal/mol in ethanol at 78 °C was obtained, i.e., much larger than that of **IA**. In the same conditions, the barrier to rotation for **3b** was measured at 28.3 kcal/mol, corresponding to a half-life for racemization of 823 days at 20 °C. These two very close results revealed that substituents in position 4 on the thiazoline ring of **3a** and **3b** produced a similar spatial requirement. Thus, despite the size of the fluorine atom, we demonstrated that a judiciously substituted *N*-(*ortho*-fluorophenyl) atropisomer could have a high enough rotational barrier to be isolated and handled without risk of racemization. These barriers are strictly originating from the steric size of the fluorine atom, and they do not involve a possible electrostatic repulsive interaction between the electron-rich fluorine atom and the flanking sulfur atom of the thiazoline-2-thione. This conclusion is firmly derived from the Cl/Me barrier ranking which was first disclosed by Colebrook et al. in 1973,[12] that is, when the barrier to rotation of an aryl ring bearing an *ortho*-Cl is larger than the barrier of the *ortho*-Me analogue, the origin of that barrier order results from an electrostatic repulsive interaction between the chlorine and a negatively charged flanking substituent. On the other hand, when the pure steric difference between a chlorine and a methyl group is operating, the barrier is larger for the methyl derivative. In thiazoline-2-thiones **IB** and **IC**, the barrier is larger for the *ortho*-methyl derivative **IC**; the same holds true for the 4-Me derivative.[13] Thus, the barriers of **3a** and **3b** are resulting from pure steric repulsion.

Table 1 outlines a proper stereoselective reaction, which discriminates on the basis of the slight difference in the steric size between hydrogen and fluorine atoms.[14] We have already shown that the stereocontrolled allylation of the anionic species derived from 2-ethylquinazolin-4-one **1** (eq 1) strongly depended on the steric influence of ortho substituents (X),[9b] that is, the diastereoselectivity decreased with decreasing bulkiness of X and completely vanished in allylation of the *ortho*-fluoro derivative **1a** (X = F, Table 1, entry 1). Since the magnitude of the diastereoselectivity might be influenced by the bulkiness of the alkyl halide as well as by the ortho substituent,[9a] the reaction of the *ortho*-fluorophenyl compound **1a** with other alkyl halides was further examined (Table 1).

Table 1. *α*-Alkylation with Quinazolinone 1a Bearing an *ortho*-Fluorophenyl Group



entry	R−Y	time (h)	**2**, **2′**	yield (%)[a]	dr 2/2′
1	allyl−Br	0.5	**2a**, **2a′**	96	1.0[b]
2	methallyl−Br	0.5	**2b**, **2b′**	86	2.0[b]
3	benzyl−Br	0.5	**2c**, **2c′**	82	2.0[c]
4	*i*-Pr−I	24	**2d**, **2d′**	84	5.4[b]
5	cyc-C_6H_{11}−I	24	**2e**, **2e′**	53	4.9[b]

[a]Isolated yield. [b]Ratio based on the isolated yield. [c]Ratio based on ^{1}H NMR analysis of the mixture of **2** and **2′**.

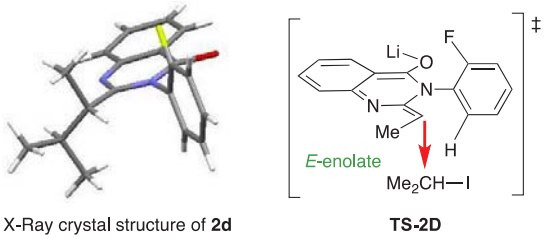
The reaction of methallyl and benzyl bromides with the anionic species prepared from **1a** (racemate) and LiHMDS at rt in THF was completed within 30 min to give the products **2b**, **2b′** and **2c**, **2c′** in good yields (86% and 82%, entries 2 and 3). In these alkylations, slight diastereoselectivity was observed (dr = 2.0). Although the reaction with bulky isopropyl iodide required a longer reaction time (24 h at rt), the products **2d** and **2d′** were obtained with good yield (84%) and moderate diastereoselectivity (**2d**/**2d′** = 5.4, entry 4). The reaction with cyclohexyl iodide also gave products **2e** and **2e′** with moderate diastereoselectivity (**2e**/**2e′** = 4.9) with a lower chemical yield (53%) due to competition with the elimination reaction (entry 5).

All of the diastereomeric products **2a−e** and **2a′−e′** shown in Table 1 were completely separated by MPLC and isolated without any isomerization at rt. Furthermore, when diastereomerically pure alkylation products **2a** and **2d** were left to stand for 1 and 24 h, respectively, under *α*-alkylation conditions (in the presence of LiHMDS in THF), no isomerization to another diastereomer was observed.[15] Thus, it is clear that the diastereomer ratios listed in Table 1 were determined by kinetic control.

One may argue that the observed diastereoselectivity is composed of steric and electrostatic contributions of the fluorine atom. The electrostatic contribution can be easily ruled out since we previously revealed that the diastereoselectivities during the allylation reaction with axially chiral quinazolinones bearing halogen (F, Cl, Br, I) and methyl groups at the ortho position were closely correlated with the van der Waals radii of the ortho substituents.[9b] The occurrence of electrostatic contribution for the halogens would have driven out the methyl group from the correlation. During the alkylation reactions reported in Table 1 the same electronic pattern is operating for all of the alkylation TS, and thus, the conclusion derived from the allylation holds for larger alkylating agents. In conclusion, the origin of the observed diastereoselectivities is mainly steric.[16]

The relative configuration of the major diastereomer **2** was determined to be (*P**,*S**) on the basis of the X-ray crystal

structural analysis of **2d** (Figure 5).[17] The diastereoselectivity can be explained as being due to the fact that the anionic



X-Ray crystal structure of **2d** **TS-2D**

Figure 5. Stereochemical assignment of **2d** and the origin of the diastereoselectivity.

species with *E*-geometry is selectively formed by treatment of **1a** with LiHMDS, and the subsequent attack of a bulky alkyl halide preferentially occurs on the opposite site of the *ortho*-fluoro group (Figure 5, **TS-2D**).

CONCLUSION

We found rare stable N−C axially chiral compounds (2-alkyl-3-arylquinazolin-4-one and 3-arylthiazoline-2-thione derivatives) bearing an *ortho*-fluorophenyl group. These have sufficient rotational stability for the enantiomer separation. A proper stereoselective α-alkylation, which discriminates on the basis of the slight steric size difference of hydrogen and fluorine atoms around N−C chiral axis, was also achieved. In addition, as shown in Figure 1,[4−6] 3-aryl-2-substituted quinazolinone derivatives are pharmaceutically attractive compounds, and our results indicate that in any drug development with quinazolin-4-one derivatives bearing an ortho-substituted phenyl group at the N3 position, the N−C axial chirality should always be considered.[18]

The occurrence of stable atropisomers in *N*-*o*-fluorophenyl derivatives and the diastereoselectivity results in the model reaction are conceptually linked, they demonstrate that the "steric" contribution of the fluorine atom becomes noticeable under strong steric demand of the nearby framework. Our findings add to the discussion on the bioisostericity of fluorine and hydrogen in drug design:[19] in terms of steric contribution, the replacement of a hydrogen by a fluorine will not be significant in the case of weak steric demand in the receptor pocket, on the contrary a noticeable steric effect is expected in the case of strong steric demand.

EXPERIMENTAL SECTION

Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. In ^{1}H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. HRMS were recorded on a double-focusing magnetic sector mass spectrometer using electron impact ionization. Column chromatography was performed on silica gel (75−150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 25 × 4 cm i.d. prepacked column (silica gel, 10 μm) with a UV detector. High-performance liquid chromatography (HPLC) was performed on a 25 × 0.4 cm i.d. chiral column with a UV detector.

3-(2-Fluorophenyl)-2-ethylquinazolin-4(3*H*)-one (1a). Under N_2 atmosphere, to 2-fluoroaniline (278 mg, 2.5 mmol) and *N*-propionyl anthranilic acid (386 mg, 2.0 mmol) in toluene (6.0 mL) was added PCl_3 (412 mg, 3.0 mmol), and the reaction mixture was stirred for 30 min at rt and for 7 h at 130 °C. The mixture was poured into water and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave **1a** (499 mg, 93%). **1a**(racemate): white solid; mp 85−86 °C; IR (neat) 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, dd, J = 1.6, 8.0 Hz), 7.72−7.80 (2H, m), 7.45−7.54 (2H, m), 7.28−7.35 (3H, m), 2.47 (2H, q, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.8, 157.7 (d, J_{C-F} = 249.8 Hz), 157.3, 147.4, 134.6, 131.3 (d, J_{C-F} = 7.6 Hz), 130.1, 127.1, 127.0, 126.6, 125.1 (d, J_{C-F} = 3.8 Hz), 124.8 (d, J_{C-F} = 14.3 Hz) 120.4, 116.9 (d, J_{C-F} = 19.0 Hz), 28.7, 10.8; MS (m/z) 291 (MNa^+); HRMS calcd for $C_{16}H_{13}FN_2NaO(MNa^+)$ 291.0910, found 291.0888. The enantiomers of **1a** were separated by HPLC using a Chiralpak AS-H column [25 cm × 0.46 cm i.d.; 15% *i*-PrOH in hexane; flow rate 0.8 mL/min, **1a**; t_R = 6.9 min, *ent*-**1a**; t_R = 9.4 min].

3-(2-Fluorophenyl)-2-methylquinazolin-4(3*H*)-one (1b). **1b** was prepared from 2-fluoroaniline (319 mg, 2.5 mmol) and *N*-acetyl anthranilic acid (358 mg, 2.0 mmol) in accordance with the procedure for the synthesis of **1a**. Purification of the residue by column chromatography (hexane/AcOEt = 2) gave **1b** (458 mg, 90%). **1b**: white solid; mp 100−102 °C; IR (neat) 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, dd, J = 1.2, 8.0 Hz), 7.76 (1H, dt, J = 1.6, 8.0 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.44−7.53 (2H, m), 7.26−7.32 (3H, m), 2.27 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7, 157.7(d, J_{C-F} = 249.8 Hz), 153.9, 147.5, 134.9, 131.5 (d, J_{C-F} = 7.6 Hz), 130.0, 127.2, 126.94, 126.87, 125.4 (d, J_{C-F} = 4.8 Hz), 125.3 (d, J_{C-F} = 15.2 Hz), 120.5, 117.1 (d, J_{C-F} = 20.0 Hz), 23.7; MS (m/z) 277 (MNa^+); HRMS calcd for $C_{15}H_{11}FN_2NaO(MNa^+)$ 277.0753, found 277.0753. The enantiomers of **1b** were separated by HPLC using chiral AS-H column [25 cm × 0.46 cm i.d.; 15% *i*-PrOH in hexane; flow rate 0.8 mL/min, **1b**; t_R = 8.5 min, *ent*-**1b**; t_R = 11.7 min].

3-(2-Fluorophenyl)-2-isopropylquinazolin-4(3*H*)-one (1c). Under N_2 atmosphere, to the solution of *rac*-**1a** (80 mg, 0.3 mmol) in THF (2.0 mL) was added THF solution of $LiN(SiMe_3)_2$ (1.3 M, 0.346 mL, 0.45 mmol) at rt, and the mixture was stirred for 30 min at rt. Iodomethane (64 mg, 0.45 mmol) was added to the mixture at rt. After being stirred for 30 min at rt, the mixture was poured into NH_4Cl aq and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave **1c** (74 mg, 87%). **1c**: white solid; mp 110−112 °C; IR (neat) 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, J = 0.8, 8.4 Hz), 7.72−7.79 (2H, m), 7.43−7.54 (2H, m), 7.28−7.35 (3H, m), 2.68 (1H, m), 1.24 (3H, d, J = 6.4 Hz), 1.23 (3H, d, J = 6.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.0, 161.1, 157.8 (d, J_{C-F} = 249.8 Hz), 147.6, 134.5, 131.2 (d, J_{C-F} = 7.6 Hz), 130.2, 127.1, 126.9, 126.5, 125.0 (d, J_{C-F} = 3.8 Hz), 124.9 (d, J_{C-F} = 13.3 Hz), 120.4, 116.9 (d, J_{C-F} = 20.0 Hz), 32.4, 21.2, 20.9; MS (m/z) 305 (MNa^+); HRMS calcd for $C_{17}H_{15}FN_2NaO(MNa^+)$ 305.1066, found 305.1062. The enantiomers of **1c** were separated by HPLC using a Chiralpak AS-H column [25 cm × 0.46 cm i.d.; 15% *i*-PrOH in hexane; flow rate 0.8 mL/min, **1c**; t_R = 6.2 min, *ent*-**1c**; t_R = 8.1 min].

(*P,*S**)- and (*P**,*R**)-3-(2-Fluorophenyl)-2-(pent-4-en-2-yl)-quinazolin-4(3*H*)-one (2a and 2a′).** Under N_2 atmosphere, to the solution of *rac*-**1a** (80 mg, 0.3 mmol) in THF (3.0 mL) was added a THF solution of $LiN(SiMe_3)_2$ (1.3 M, 0.346 mL, 0.45 mmol) at rt, and the mixture was stirred for 30 min at rt. Allyl bromide (54 mg, 0.45 mmol) was added to the mixture at rt. After being stirred for 30 min at rt, the mixture was poured into NH_4Cl aq and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave mixtures of **2a** and **2a′** (85 mg, 96%). The diastereomer ratio of **2a** and **2a′** (1:1) was determined on the basis of isolated yield. **2a** and **2a′** were completely separated by medium-pressure liquid chromatography (MPLC, eluent hexane/AcOEt = 8) to give diastereomerically pure **2a** and **2a′** (40 mg, 43% and 41 mg, 44%). **2a**: white solid; mp 77−80 °C; IR (neat) 1692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, J = 1.2, 7.6 Hz), 7.73−7.80 (2H, m), 7.44−7.54 (2H, m), 7.24−7.35 (3H, m), 5.62 (1H, m), 4.98 (1H, dd, J = 1.2, 16.8 Hz), 4.94 (1H, dd, J = 2.0, 10.0 Hz), 2.57−2.68 (2H, m), 2.23 (1H, m), 1.23

(3H, d, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 159.9, 157.9 (d, J_{C-F} = 249.9 Hz), 147.6, 135.7, 134.6, 131.2 (d, J_{C-F} = 7.7 Hz), 130.7, 127.2, 127.0, 126.6, 125.0 (d, J_{C-F} = 3.8 Hz), 124.8 (d, J_{C-F} = 13.4 Hz), 120.4, 117.1, 116.9 (d, J_{C-F} = 20.0 Hz), 39.8, 37.9, 19.1; MS (m/z) 331 (MNa^+); HRMS calcd for $C_{19}H_{17}FN_2NaO$(MNa^+) 331.1223, found 331.1203. **2a′**: white solid; mp 86−88 °C; IR (neat) 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, dd, J = 1.2, 7.6 Hz), 7.72−7.80 (2H, m), 7.52 (1H, m), 7.46 (1H, ddd, J = 1.2, 6.8, 7.6 Hz), 7.27−7.35 (3H, m), 5.62 (1H, m), 4.97 (1H, d, J = 17.2 Hz), 4.94 (1H, d, J = 10.0 Hz), 2.65 (1H, td, J = 6.4, 13.6 Hz), 2.55 (1H, sext, J = 6.4 Hz), 2.34 (1H, td, J = 6.8, 13.6 Hz), 1.23 (3H, d, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 159.9, 157.8 (d, J_{C-F} = 249.8 Hz), 147.6, 135.6, 134.6, 131.3 (d, J_{C-F} = 7.7 Hz), 130.1, 127.2, 127.0, 126.6, 125.1 (d, J_{C-F} = 3.8 Hz), 124.9 (d, J_{C-F} = 13.3 Hz), 120.4, 116.9 (d, J_{C-F} = 20.0 Hz), 116.9, 39.3, 38.0, 19.2; MS (m/z) 331 (MNa^+); HRMS calcd for $C_{19}H_{17}FN_2NaO$-(MNa^+) 331.1223, found 331.1196.

(*P,*S**)- and (*P**,*R**)-3-(2-Fluorophenyl)-2-(4-methylpent-4-ene-2-yl)quinazolin-4(3*H*)-one (2b and 2b′).** **2b** and **2b′** were prepared from *rac*-**1a** (80 mg, 0.3 mmol) and methallyl bromide (61 mg, 0.45 mmol) in accordance with the procedure for synthesis of **2a** and **2a′**. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave mixtures of **2b** and **2b′**(84 mg, 86%). **2b** and **2b′** were completely separated by MPLC (hexane/AcOEt = 7) to give diastereomerically pure **2b** and **2b′** (50 mg, 52%; 24 mg, 25%). The diastereomeric ratio of **2b** and **2b′** (2:1) was determined on the basis of the isolated yield. **2b**: white solid; mp 84−86 °C; IR (neat) 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, J = 1.2, 8.4 Hz), 7.72−7.80 (2H, m), 7.44−7.54 (2H, m), 7.27−7.36 (3H, m), 4.69 (1H, d, J = 1.6 Hz), 4.61 (1H, d, J = 1.6 Hz), 2.71 (1H, m), 2.60 (1H, dd, J = 6.4, 13.6 Hz), 2.15 (1H, dd, J = 6.8, 13.6 Hz), 1.42 (3H, s), 1.22 (3H, d, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 160.2, 157.9 (d, J_{C-F} = 249.8 Hz), 147.6, 142.6, 134.6, 131.2 (d, J_{C-F} = 7.6 Hz), 130.6, 127.2, 127.0, 126.5, 125.0 (d, J_{C-F} = 3.9 Hz), 124.8 (d, J_{C-F} = 13.3 Hz), 120.4, 116.9 (d, J_{C-F} = 20.0 Hz), 112.9, 43.6, 36.1, 22.1, 18.6; MS (m/z) 345 (MNa^+); HRMS calcd for $C_{20}H_{19}FN_2NaO$(MNa^+) 345.1379, found 345.1358. **2b′**: white solid; mp 92−94 °C; IR (neat) 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.28 (1H, dd, J = 1.6, 8.4 Hz), 7.71−7.80 (2H, m), 7.44−7.55 (2H, m), 7.28−7.37 (3H, m), 4.70 (1H, s), 4.63 (1H, s), 2.70 (1H, m), 2.53 (1H, dd, J = 5.6, 14.0 Hz), 2.19 (1H, dd, J = 8.8, 14.0 Hz), 1.40 (3H, s), 1.21 (3H, d, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 162.0, 160.2, 157.9 (d, J_{C-F} = 250.8 Hz), 147.6, 142.4, 134.6, 131.3 (d, J_{C-F} = 7.6 Hz), 130.2, 127.2, 127.0, 126.6, 125.1 (d, J_{C-F} = 3.9 Hz), 124.9 (d, J_{C-F} = 13.3 Hz), 120.4, 116.9 (d, J_{C-F} = 19.1 Hz), 113.0, 43.3, 35.9, 21.6, 18.5; MS (m/z) 345 (MNa^+); HRMS calcd for $C_{20}H_{19}FN_2NaO$(MNa^+) 345.1379, found 345.1356.

(*P,*S**)- and (*P**,*R**)-3-(2-Fluorophenyl)-2-(1-phenylpropan-2-yl)quinazolin-4(3*H*)-one (2c and 2c′).** **2c** and **2c′** were prepared from *rac*-**1a** (80 mg, 0.3 mmol) and benzyl bromide (77 mg, 0.45 mmol) in accordance with the procedure for synthesis of **2a** and **2a′**. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave mixtures of **2c** and **2c′** (88 mg, 82%). **2c** and **2c′** were completely separated by MPLC (hexane/AcOEt = 8) to give diastereomerically pure **2c** and **2c′** (50 mg, 47%; 32 mg, 30%). The diastereomeric ratio of **2c** and **2c′** (2:1) was determined on the basis of ^1H NMR analysis. **2c**: colorless oil; IR (neat) 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 7.6 Hz), 7.80−7.84 (2H, m), 7.44−7.52 (2H, m), 7.26 (1H, t, J = 8.0 Hz), 7.15−7.21 (3H, m), 7.15 (1H, t, J = 8.0 Hz), 6.90−6.92 (2H, m), 6.36 (1H, dt, J = 2.0, 8.0 Hz), 3.26 (1H, dd, J = 8.0, 12.4 Hz), 2.80 (1H, m), 2.74 (1H, dd, J = 5.2, 12.4 Hz), 1.33 (3H, d, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.8, 159.9, 157.8 (d, J_{C-F} = 249.8 Hz), 147.6, 139.7, 134.6, 131.0 (d, J_{C-F} = 7.7 Hz), 130.6, 129.0, 128.3, 127.2, 127.0, 126.6, 126.3, 124.9 (d, J_{C-F} = 3.9 Hz), 124.6 (d, J_{C-F} = 13.4 Hz), 120.4, 116.5 (d, J_{C-F} = 19.1 Hz), 42.3, 40.6, 19.7; MS (m/z) 381 (MNa^+); HRMS calcd for $C_{23}H_{19}FN_2NaO$(MNa^+) 381.1379, found 381.1352. **2c′**: white solid; mp 114−117 °C; IR (neat) 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, dd, J = 0.8, 7.2 Hz), 7.78−7.83 (2H, m), 7.55 (1H, m), 7.49 (1H, m), 7.29−7.37 (3H, m), 7.14−7.22 (3H, m), 6.92−6.94 (2H, m), 3.20 (1H, dd, J = 4.4, 12.4 Hz), 2.78 (1H, m), 2.74 (1H, dd, J = 8.8, 12.4 Hz), 1.22 (3H, d, J = 6.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 159.9, 157.9 (d, J_{C-F} = 250.7 Hz), 147.5, 139.5, 134.6, 131.4 (d, J_{C-F} = 7.6 Hz), 130.2, 129.0, 128.2, 127.2, 127.0, 126.7, 126.2, 125.1 (d, J_{C-F} = 3.9 Hz), 124.8 (d, J_{C-F} = 13.3 Hz), 120.5, 116.9 (d, J_{C-F} = 19.1 Hz), 41.2, 40.1, 18.5; MS (m/z) 381 (MNa^+); HRMS calcd for $C_{23}H_{19}FN_2NaO$(MNa^+) 381.1379, found 381.1353.

(*P,*S**)- and (*P**,*R**)-3-(2-Fluorophenyl)-2-(3-methylbutan-2-yl)quinazolin-4(3*H*)-one (2d and 2d′).** Under N_2 atmosphere, to the solution of *rac*-**1a** (268 mg, 1 mmol) in THF (3.0 mL) was added a THF solution of $LiN(SiMe_3)_2$ (1.3 M, 1.15 mL, 1.5 mmol) at rt, and the mixture was stirred for 30 min at rt. Isopropyl iodide (255 mg, 1.5 mmol) was added to the mixture at rt. After being stirred for 24 h at rt, the mixture was poured into NH_4Cl aq and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 6) gave the mixtures of **2d** and **2d′** (260 mg, 84%). **2d** and **2d′** were completely separated by MPLC (hexane/AcOEt = 8) to give diastereomerically pure **2d** and **2d′** (202 mg, 65% and 37 mg, 12%). The diastereomeric ratio of **2d** and **2d′** (5.4:1) was determined on the basis of the isolated yield. **2d**: white solid; mp 155−158 °C; IR (neat) 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 7.6 Hz), 7.71−7.76 (2H, m), 7.41−7.51 (2H, m), 7.26−7.34 (3H, m), 2.12−2.25 (2H, m), 1.22 (3H, d, J = 6.0 Hz), 0.88 (3H, d, J = 5.6 Hz), 0.81 (3H, d, J = 6.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 160.8, 157.8 (d, J_{C-F} = 248.8 Hz), 147.6, 134.4, 131.1 (d, J_{C-F} = 8.6 Hz), 130.9, 127.2, 126.9, 126.4, 125.1 (d, J_{C-F} = 14.3 Hz), 125.0 (d, J_{C-F} = 3.9 Hz), 120.4, 116.9 (d, J_{C-F} = 19.0 Hz), 44.4, 32.6, 21.6, 19.0, 16.8; MS (m/z) 333 (MNa^+); HRMS calcd for $C_{19}H_{19}FN_2NaO$(MNa^+) 333.1379, found 333.1393. **2d′**: white solid; mp 145−150 °C; IR (neat) 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, dd, J = 0.8, 8.0 Hz), 7.70−7.79 (2H, m), 7.44−7.55 (2H, m), 7.24−7.34 (3H, m), 2.10−2.20 (2H, m), 1.21 (3H, d, J = 6.4 Hz), 0.87 (3H, d, J = 6.4 Hz), 0.80 (3H, d, J = 6.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 160.9, 157.8 (d, J_{C-F} = 249.8 Hz), 147.7, 134.6, 131.3 (d, J_{C-F} = 7.6 Hz), 129.8, 127.2, 127.0, 126.5, 125.2 (d, J_{C-F} = 13.4 Hz), 125.1 (d, J_{C-F} = 3.8 Hz), 120.4, 116.9 (d, J_{C-F} = 19.1 Hz), 45.0, 31.9, 21.5, 19.3, 17.4; MS (m/z) 333 (MNa^+); HRMS calcd for $C_{19}H_{19}FN_2NaO$(MNa^+) 333.1379, found 333.1373.

(*P,*S**)- and (*P**,*R**)-3-(2-Fluorophenyl)-2-(1-cyclohexylethyl)quinazolin-4(3*H*)-one (2e and 2e′).** **2e** and **2e′** were prepared from *rac*-**1a** (268 mg, 1 mmol) and cyclohexyl iodide (315 mg, 1.5 mmol) in accordance with the procedure for synthesis of **2d** and **2d′**. Purification of the residue by column chromatography (hexane/AcOEt = 6) gave mixtures of **2e** and **2e′** (186 mg, 53%). **2e** and **2e′** were completely separated by MPLC (hexane/AcOEt = 8) to give diastereomerically pure **2e** and **2e′** (142 mg, 41% and 29 mg, 8%). The diastereomeric ratio of **2e** and **2e′** (4.9:1) was determined on the basis of the isolated yield. **2e**: white solid; mp 129−133 °C; IR (neat) 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, J = 1.2, 8.0 Hz), 7.72−7.79 (2H, m), 7.44−7.54 (2H, m), 7.25−7.37 (3H, m), 2.22 (1H, quint, J = 6.8 Hz), 1.80−1.89 (2H, m), 1.53−1.72 (4H, m), 1.03−1.28 (3H, m), 1.20 (3H, d, J = 6.8 Hz), 0.67−0.85 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1, 161.1, 157.9 (d, J_{C-F} = 249.8 Hz), 147.8, 134.5, 131.1 (d, J_{C-F} = 7.6 Hz), 131.0, 127.2, 127.0, 126.4, 125.1 (d, J_{C-F} = 13.4 Hz), 125.0 (d, J_{C-F} = 3.8 Hz), 120.3, 116.9 (d, J_{C-F} = 20 Hz), 43.7, 42.4, 32.1, 29.6, 26.32, 26.30, 26.1, 16.8; MS (m/z) 373 (MNa^+); HRMS calcd for $C_{22}H_{23}FN_2NaO$(MNa^+) 373.1692, found 373.1676. **2e′**: colorless oil; IR (neat) 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, dd, J = 0.8, 8.4 Hz), 7.71−7.79 (2H, m), 7.44−7.55 (2H, m), 7.22−7.34 (3H, m), 2.18 (1H, quint, J = 6.8 Hz), 1.82−1.89 (2H, m), 1.52−1.71 (4H, m), 1.02−1.28 (3H, m), 1.20 (3H, d, J = 6.4 Hz), 0.70−0.80 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 161.0, 157.8 (d, J_{C-F} = 250.8 Hz), 147.7, 134.6, 131.3 (d, J_{C-F} = 8.5 Hz), 129.7, 127.2, 127.0, 126.5, 125.2 (d, J_{C-F} = 13.3 Hz), 125.1 (d, J_{C-F} = 3.8 Hz), 120.3, 116.9 (d, J_{C-F} = 19.1 Hz), 43.9, 41.4, 31.7, 29.5, 26.31, 26.27, 26.2, 17.0; MS (m/z) 373

(MNa^+); HRMS Calcd for $C_{22}H_{23}FN_2NaO(MNa^+)$ 373.1692, found 373.1667.

General Procedure for Synthesis of 3a and 3b. Distilled triethylamine (40 mmol) was added dropwise under nitrogen atmosphere to a solution of *ortho*-fluoroaniline (20 mmol) in carbon disulfide (38 mL). The mixture was stirred at rt overnight. Then the precipitate was filtered, washed with Et_2O, and dried to give the dithiocarbamate salt as a light yellow solid. This salt was used without any further purification and immediately solubilized in acetonitrile (31 mL). 2-Chlorocyclohexanone (20 mmol) for **3a** or 2-chloroacetone (20 mmol) for **3b** was then added dropwise at rt under nitrogen atmosphere. The mixture was stirred 24 h at rt. Then a 37% HCl solution (5 mL) was added dropwise, and the mixture was heated at reflux (oil bath) for 20 min. The solvent was evaporated under reduced pressure, and water was added (50 mL). The mixture was extracted with dichloromethane (3 × 50 mL); the organic layer was dried on $MgSO_4$ and evaporated under reduced pressure. The desired product was purified by flash chromatography (petroleum ether−dichloromethane, 60/40 → 0/100).

*3-(2-Fluorophenyl)-4,5,6,7-tetrahydro-1,3-benzothiazole-2(3H)-thione (**3a**).* Yield: 82% (4.4 g); white solid; mp 162.4−164.8 °C (racemate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62−1.86 (4H, m, 2 CH_2), 2.11−2.12 (2H, m, CH_2), 2.52−2.53 (2H, m, CH_2), 7.28−7.33 (3H, m, arom), 7.47−7.53 (1H, m, arom); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_2), 22.6 (CH_2), 23.1 (CH_2), 24.3 (CH_2), 117.0 (d, CH, J = 19.1), 120.8 (CH), 124.9 (d, C, J = 12.8), 125.0 (d, CH, J = 3.8), 130.3 (C), 131.5 (d, CH, J = 7.8), 137.1 (C), 157.2 (d, C, J = 253.0), 188.6 (C); HRMS (ESI/TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{13}NS_2F$ 266.0468, found 266.0471. Chiral HPLC: Whelk-O1 (*S,S*), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, R_{t_1} = 6.72 min (−), R_{t_2} = 8.26 min (+), k_1 = 1.24, k_2 = 1.75, α = 1.41, and R_s = 4.16. First eluted (99% ee): $[\alpha]_D^{25}$ −95.7 (c 0.82, $CHCl_3$).

*3-(2-Fluorophenyl)-4-mêthylthiazole-2(3H)-thione (**3b**).* **3b** was prepared in accordance with the procedure for the synthesis of **3a**. Yield: 85% (3.8 g); white solid; mp 145−147 °C (racemate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, s, CH_3), 6.36 (1H, s, CH), 7.25−7.36 (3H, m, arom), 7.47−7.54 (1H, m, arom); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 106.4 (CH), 117.1 (d, CH, J = 19.2), 125.2 (d, C, J = 13.2), 125.3 (d, CH, J = 3.8), 130.4 (CH), 131.9 (d, CH, J = 7.7), 139.9 (C), 157.4 (d, C, J = 252.4), 190.5 (C); HRMS (ESI/TOF) m/z $[M + H]^+$ calcd for $C_{10}H_9NS_2F$ 226.0155, found 226.0153. Chiral HPLC: Whelk-O1 (*S,S*), 30 °C, hexane/2-PrOH 80/20, 1 mL/min, UV, R_{t_1} = 12.5 min, R_{t_2} = 18.1, k_1 = 3.2, k_2 = 5.0, α = 1.58, and R_s = 6.96. First eluted (99.5% ee): $[\alpha]_D^{25}$ −107 (c 0.51, $CHCl_3$).

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