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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. 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, 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.

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). 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. Furthermore, although the antiviral quinazolinone shown in Figure 1, IVA, is also well known, there is no report of its N–C axial chirality. 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 (t1/2 = 1.4 days at 298 K).
As shown in eq 1, we recently reported the \( \alpha \)-alkylation of anionic species prepared from \( N \equiv C \) axially chiral 2-ethyl-

\[
\begin{align*}
\text{N} & \equiv \text{C} \equiv \text{N} \\
\text{Me} & \equiv \text{C} \equiv \text{Me}
\end{align*}
\]

quinazolin-4-ones bearing various ortho-substituted phenyl groups on the nitrogen atom.\(^7\) The reaction proceeded with stereocontrol due to axial chirality to preferentially afford the products 2 with a \((F, S)\)-configuration.

In the course of this work, it was found that no \( N \equiv C \) bond rotation occurs in the diastereomeric alkylation product 2a (\( X = F, R = \text{allyl} \)) bearing an \( ortho \)-fluorophenyl group even after standing for 24 h at rt in THF (eq 1).\(^8\) The unexpected rotational stability of 2a aroused our interest for the atropisomerism resulting from fluorne as a blocking substituent and for experimental evidence of the steric discrimination between the two smallest substituents: fluorne and hydrogen. In this article, we discuss several rare \( N \equiv C \) axially chiral compounds (3-arylquinazolin-4-ones and 3-aryltiazoline-2-thiones) bearing a \( C_2 \) 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-fluorophenol, 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 \( CC_l \), and these data were subjected to an Eyring plot to determine the rotational barriers (Figure 2 and see SI).

![Figure 2. Rotational barriers and half-life time of quinazolinones 1a–c at 25 °C in \( CC_l \)](image)

The rotational barrier and half-life time for the racemization of the 2-ethyl derivative 1a at 298 K in \( CC_l \) 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 \( N \equiv C \) bond rotation of the anionic species prepared from quinazolinone VIIID with an \( ortho \)-bromophenyl group occurs easily at ambient temperature, in remarkable contrast with neutral VIIID, which presents a high rotational barrier (ca. \( \Delta G^\ddagger = 35 \text{ kcal/mol} \)).\(^9\) The structure of quinazolinone IIIA with an alkylthio group at C2 may be similar to the anionic species of VIIID 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 VIIID. Meanwhile, since the rotational barriers of quinazolinones bearing an \( ortho \)-fluorophenyl group are not so high (ca. \( \Delta G^\ddagger = 26 \text{ kcal/mol} \)), 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 VIIID. 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 \( N \equiv C \) 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,\(^8\) we designed other \( N \equiv C \) 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 (\( \Delta G^\ddagger = 19.7 \text{ kcal/mol} \), Figures 1 and 4).\(^7\) In order to increase the rotational barrier by structural modification, we envisioned the
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,\(^{12}\) compared to the 131° found for the five-membered ring analogues,\(^{13}\) making the rotation about the pivotal bond more difficult in the first case. Thus, the targeted cyclohexame 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 \(\Delta G^\circ\) value of 27.9 kcal/mol in ethanol at 78 °C was obtained, i.e., much larger than that of 1a. 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 1B and 1C, 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 alkylation of the anionic species derived from 2-ethylquinazolin-4-one 1 (eq 1) strongly depended on the steric influence of ortho substituents (X),\(^{15}\) that is, the diastereoselectivity decreased with decreasing bulkiness of X and completely vanished in alkylation of the ortho-fluoro derivative 1a (\(X = \text{F, Table 1, entry 1}\)). Since the magnitude of the diastereoselectivity might be influenced by the bulkiness of the alkyl halide as well as by the ortho substituent,\(^{16}\) the reaction of the ortho-fluorophenyl compound 1a with other alkyl halides was further examined (Table 1).

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 alkylation, 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 \(\alpha\)-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 alkylation 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.\(^{16}\) 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 alkylation 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 (\(P^\alpha,S^\beta\)) on the basis of the X-ray crystal
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-fluoroaryl 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 fluorne atoms around N=C chiral axis, was also achieved. In addition, as shown in Figure 1, 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.

The occurrence of stable atropisomers in N-α-fluorophenyl derivatives and the diastereoselectivity results in the model reaction are conceptually linked, they demonstrate that the "steric" contribution of the fluorne atom becomes noticeable under strong steric demand of the nearby framework. Our findings add to the discussion on the bioisostericity of hydrogen and fluorne in drug design in terms of steric contribution, the replacement of a hydrogen by a fluorne 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. 1H and 13C NMR spectra were recorded on a 400 MHz spectrometer. In 1H and 13C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from CHCl3 (7.26 ppm) and CDCl3 (77.0 ppm), respectively. HRMS were recorded on a double-focusing magnetic sector mass spectrometer. In 1H and 13C NMR spectra, 1H NMR (400 MHz, CDCl3) δ 6.7 (1H, d, J = 1.6, 8.0 Hz), 7.32–7.79 (2H, m), 7.43–7.54 (2H, m), 7.78–7.85 (3H, m), 2.68 (1H, m), 1.24 (3H, d, J = 6.4 Hz), 1.23 (3H, d, J = 6.4 Hz); 13C (1H) NMR (100 MHz, CDCl3) δ 8.27 (1H, d, J, f = 294.8 Hz), 147.6, 134.5, 131.2 (d, J, f = 7.6 Hz), 147.6, 134.5, 131.2 (d, J, f = 7.6 Hz), 120.5, 117.1 (d, J, f = 15.2 Hz), 120.5, 117.1 (d, J, f = 15.2 Hz), 20.7; MS (m/z) 277 (M+Na+); HRMS calcd for C15H11FN2NaO (M+Na+) 277.0753, found 277.0752. 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; tR = 6.9 min, ent-1a; tR = 9.4 min].

(3-Fluorophenyl)-2-methylquinazolin-4(3H)-one (1b). 1b was prepared from 2-fluoroaniline (319 mg 2.5 mmol) and N-acetyl anilinic acid (356 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) 1684 cm–1; 1H NMR (400 MHz, CDCl3) δ 6.7 (1H, d, J = 1.6, 8.0 Hz), 7.32–7.79 (2H, m), 7.43–7.54 (2H, m), 7.78–7.85 (3H, m), 2.47 (2H, q, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz); 13C (1H) NMR (100 MHz, CDCl3) δ 135.2, 131.1, 120.4, 116.9 (d, J, f = 19.0 Hz), 28.7, 10.8; MS (m/z) 291 (M+Na+); HRMS calcd for C16H13FN2NaO (M+Na+) 291.0910, found 291.0888. The diastereomer ratio of 1a 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 diastereomically pure 2a and 2a’ (40 mg, 43% and 41 mg, 44%). 2a: white solid; mp 77–80 °C; IR (neat) 1692 cm–1; 1H NMR (400 MHz, CDCl3) δ 8.27 (1H, dd, J = 1.2, 7.6 Hz), 7.32–7.80 (2H, m), 7.44–7.54 (2H, m), 7.24–7.35 (3H, m), 5.62 (1H, m), 4.98 (1H, dd, f = 1.2, 16.8 Hz), 4.94 (1H, dd, f = 2.0, 10.0 Hz), 2.57–2.68 (2H, m), 2.23 (1H, m), 1.23

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; 1H NMR (400 MHz, CDCl3) 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); 13C (1H) NMR (100 MHz, CDCl3) δ 161.8, 157.7 (d, J, f = 249.8 Hz), 157.3, 147.4, 134.6, 131.3 (d, J, f = 7.6 Hz), 130.1, 127.1, 127.0, 126.6, 126.5, 126.1 (d, J, f = 3.8 Hz), 124.8 (d, J, f = 14.3 Hz) 120.4, 116.9. 4 cm i.d.; chiral column with a UV detector. High-performance liquid chromatography (HPLC) was performed on a 25 cm × 0.46 cm i.d. chiral column with a UV detector. Medium-pressure liquid chromatography (MPLC, eluent hexane/AcOEt = 8) gave diastereomically pure 2a and 2a’ (40 mg, 43% and 41 mg, 44%). 2a: white solid; mp 77–80 °C; IR (neat) 1692 cm–1; 1H NMR (400 MHz, CDCl3) 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, f = 1.2, 16.8 Hz), 4.94 (1H, dd, f = 2.0, 10.0 Hz), 2.57–2.68 (2H, m), 2.23 (1H, m), 1.23

![X-Ray crystal structure of 2d](Image)

**Figure 5.** Stereochemical assignment of 2d and the origin of the diastereoselectivity.
7.15 (1H, t, J = 2.0 Hz), 6.92–6.94 (2H, m), 3.20 (1H, dd, J = 4.4, 12.4 Hz), 2.78 (1H, d, J = 8.8, 12.4 Hz), 1.22 (3H, d, J = 6.4 Hz); 186 mg, 33%, 32 mg, 30%). The diastereomeric ratio of 2e and 2f (2:1) was determined on the basis of the isolated yield. 2e white solid; mp 115.8 °C; IR (neat) 1684 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 8.27 (1H, dd, J = 1.2, 7.6 Hz, 7.72–7.80 (2H, m), 7.52 (1H, m), 7.46 (1H, dd, J = 1.2, 6.8, 7.6 Hz), 7.27–7.35 (3H, m), 5.62 (1H, m), 4.97 (1H, J = 17.2 Hz), 4.94 (1H, J = 10.0 Hz), 2.65 (1H, td, J = 6.4, 13.6 Hz), 2.55 (1H, s, J = 6.4 Hz), 2.34 (1H, td, J = 6.8, 13.6 Hz), 1.23 (3H, d, J = 6.4 Hz); 13C(H) NMR (100 MHz, CDCl₃) δ 162.0, 159.7, 158.1, 147.6, 135.6, 134.6, 131.3 (d, J = 16.4 Hz, 17.3 Hz), 130.1, 127.2, 120.7, 126.6, 125.1 (d, J = 13.6 Hz, 13.4 Hz, 12.0, 146.5, 116.9 (d, J = 20.0 Hz), 116.9, 39.3, 38.0, 19.2; MS (m/z) 331 (M⁺); HRMS calc for C₂₁H₁₉FN₄O₃Na⁺ 331.1379, found 331.1397.

(P*(S)⁺) and (P*(R)⁺)-3-(2-Fluorophenyl)-2-(3-methylbutan-2-yl)quinazolin-4(3H)-one (2d and 2f). Under N₂ atmosphere, to the solution of rac-1a (268 mg, 1 mmol) in THF (3.0 mL) was added a THF solution of Li(N(Me₂)₂) (1.3 M, 1.15 mL, 1.5 mmol) at rt, and the mixture was stirred for 30 min at rt. Isopropl iodide (255 mg, 1.5 mmol) was added to the mixture at rt. After being stirred for 2 h at rt, the mixture was poured into NH₄Claq and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over MgSO₄, and evaporated to dryness. Purification of the residue by column chromatography (hexane/acetone = 6) gave the mixtures of 2d and 2f (260 mg, 84%). The diastereomeric ratio of 2d and 2f (5:4) was determined on the basis of the isolated yield. 2d white solid; mp 153.0 °C; IR (neat) 1684 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 8.27 (1H, dd, J = 1.2, 7.6 Hz, 7.71–7.77 (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 = 6.0 Hz), 0.81 (3H, d, J = 6.0 Hz); 186 mg, 53%, 32 mg, 30%). The diastereomeric ratio of 2e and 2f (4:9:1) was determined on the basis of the isolated yield. 2e white solid; mp 117–133 °C; IR (neat) 1669 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 8.27 (1H, dd, J = 1.2, 8.0 Hz), 7.72–7.79 (2H, m), 7.44–7.54 (2H, m), 7.71–7.80 (2H, m), 7.45–7.55 (2H, m), 7.28–7.37 (3H, m), 4.70 (1H, s), 4.63 (1H, s), 2.70 (1H, m), 2.53 (1H, t, J = 6.6, 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); 13C(H) NMR (CDCl₃) δ 110.8, 106.2, 105.9 (d, J = 250.0 Hz, CDCl₃) δ 147.6, 142.4, 134.6, 131.3 (d, J = 16.4 Hz, 17.3 Hz), 130.0, 127.2, 120.7, 126.5, 125.0 (d, J = 13.6 Hz, 13.4 Hz, 12.0, 116.9 (d, J = 20.0 Hz), 116.9, 43.0, 35.9, 21.6, 18.5; MS (m/z) 345 (M⁺); HRMS calc for C₂₁H₂₁FN₄NaO₃⁺ 345.1379, found 345.1388. 2d: white solid; mp 145–150 °C; IR (neat) 1686 cm⁻¹; 1H NMR (400 MHz, CDCl₃) 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 (10H, 2H, d, J = 6.0 Hz); 13C(H) NMR (CDCl₃) δ 147.7, 143.6, 134.3, 131.3 (d, J = 16.4 Hz, 17.3 Hz), 129.8, 127.2, 120.7, 126.5, 125.2 (d, J = 13.4 Hz, 12.0, 116.9 (d, J = 20.0 Hz), 43.7, 42.4, 32.1, 29.6, 26.32, 26.30, 26.1, 16.8; MS (m/z) 333 (M⁺); HRMS calc for C₂₃H₂₃FN₄NaO₃⁺ 333.1379, found 333.1373.

(P*(S)⁺) and (P*(R)⁺)-3-(2-Fluorophenyl)-2-(1-cyclohexylethyl)quinazolin-4(3H)-one (2b and 2f). The mixture of 2b and 2f was completely separated by MPLC (hexane/acetone = 7) to give diastereomerically pure 2b and 2f (50 mg, 52%; 32 mg, 24% yield). The diastereomic ratio of 2b and 2f (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, CDCl₃) δ 8.27 (1H, dd, J = 1.2, 7.6 Hz, 7.72–7.80 (2H, m), 7.52 (1H, m), 7.46 (1H, dd, J = 1.2, 6.8, 7.6 Hz), 7.27–7.35 (3H, m), 5.62 (1H, m), 4.97 (1H, J = 17.2 Hz), 4.94 (1H, J = 10.0 Hz), 2.65 (1H, td, J = 6.4, 13.6 Hz), 2.55 (1H, s, J = 6.4 Hz), 2.34 (1H, td, J = 6.8, 13.6 Hz), 1.23 (3H, d, J = 6.4 Hz); 13C(H) NMR (100 MHz, CDCl₃) δ 162.0, 159.7, 158.1, 147.6, 135.6, 134.6, 131.3 (d, J = 16.4 Hz, 17.3 Hz), 130.1, 127.2, 120.7, 126.6, 125.1 (d, J = 13.6 Hz, 13.4 Hz, 12.0, 146.5, 116.9 (d, J = 20.0 Hz), 116.9, 39.3, 38.0, 19.2; MS (m/z) 331 (M⁺); HRMS calc for C₂₁H₁₉FN₄NaO₃⁺ 331.1379, found 331.1396.
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 Et₂O, and dried to give the dithiocarbamate salt as a light yellow solid. This salt was used without 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 MgSO₄ and evaporated under reduced pressure. The desired product was purified by flash chromatography (petroleum ether–dichloromethane, 60/40 → 0/100).

3-(2-Fluorophenyl)-4-methylthiazole-2(3H)-thione (3a). Yield: 82% (14.4 g); white solid; mp 162.4 °C. 1H NMR (400 MHz, CDCl₃) δ 7.54 (1H, m, arom); 13C{1H} NMR 7.36 (3H, m, arom), 7.47 (1H, s, CH), 2.12 (2H, m, CH₂), 2.52–2.53 (2H, m, CH₂), 7.28–7.33 (3H, m, arom), 7.47–7.53 (1H, m, arom); 13C{1H} NMR (100 MHz, CDCl₃) δ 21.6 (CH₂), 22.6 (CH₂), 23.1 (CH₂), 24.3 (CH₂), 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 C₁₂H₁₂FNO (MNa+) 225.0579, found 225.0644. 1H NMR (600 MHz, CDCl₃) δ 0.51, CHCl₃.

3-(2-Fluorophenyl)-4-methylthiazole-2(3H)-thione (3b). Yield: 85% (3.8 g); white solid; mp 145–147 °C (racemate); 1H NMR (400 MHz, CDCl₃) δ 1.95 (3H, s, CH₃), 6.36 (1H, s, CH), 7.25–7.36 (3H, m, arom), 7.47–7.54 (1H, m, arom); 13C{1H} NMR (100 MHz, CDCl₃) δ 15.4 (CH₃), 106.4 (CH), 117.1 (d, CH, J = 19.2), 125.2 (d, C, J = 13.2), 125.3 (d, CH, J = 3.8), 131.4 (d, CH, J = 7.7), 137.9 (C), 157.4 (d, C, J = 252.4), 190.5 (C). HRMS (ESI/TOF) m/z [M + H]+ calcd for C₂₂H₂₃FN₂O(MNa+) 373.1692, found 373.1692.


(53) When diastereomerically pure 2a, 2c, and 2e were heated for 8 h at 80 °C in toluene, equilibrium mixtures of the diastereomers (2a/2c = 1, 2e/2e' = 1.8, and 2e/2e'' = 3.5) were obtained. (f) Miller, S. J. Enantioselective Synthesis of 3-Arylquinazolin-4(3H)-thiones by Separation of Enantiomers and Barriers to Racemization. J. Chem. Soc., Perkin Trans. 2 1990, 619.


(10) Miller et al. evaluated that the rotational barrier of 2-methyl-3-(2-fluorophenyl)quinazolin-4-one is ca. 26 kcal/mol by DFT calculation, while the experimental value has not been described: (a) Dimer, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. Enantioselective Synthesis of 3-Arylquinazolin-4(3H)-ones via Peptide-Catalyzed Atroposelective Bromination. J. Am. Chem. Soc. 2015, 137, 12369.
