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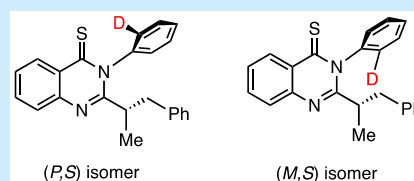
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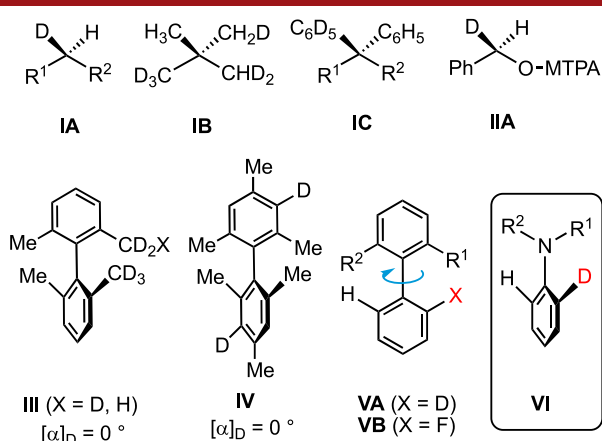
# Detection of Isotopic Atropisomerism Based on *ortho*-H/D Discrimination

Kazuya Saito, Shota Miwa, Asumi Iida, Yuuki Fujimoto, Elsa Caytan, Christian Roussel, and Osamu Kitagawa\*

**ABSTRACT:** Racemic and optically active 3-(2-deuteriophenyl)-2-(1-phenylpropan-2-yl)quinazoline-4-thiones were prepared. The nuclear magnetic resonance spectra clearly show that they exist as a 1:1 mixture of diastereomers due to the isotopic atropisomerism based on *ortho*-H/D discrimination (N–C axial chirality) and a chiral carbon.



Organic compounds containing deuterium atoms have been used widely as probe molecules for the elucidation of reaction mechanisms, metabolic pathways, and biosynthetic pathways as well as solvents for nuclear magnetic resonance (NMR) measurement.<sup>1</sup> Furthermore, partially deuterated analogues of approved medicinal drugs have recently received much attention because they lead to an increase in pharmacological action and an extended duration of action.<sup>2</sup> Isotopically chiral compounds based on deuterium atoms such as **IA–IC** have also been encountered (Figure 1).<sup>3</sup> These chiral



**Figure 1.** Various isotopically chiral compounds due to the deuterium atom.

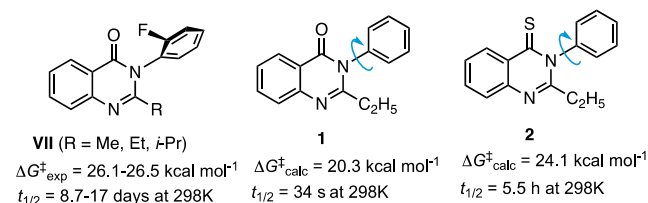
deuterated compounds not only are intriguing from the viewpoint of structural chemistry but also have been used for mechanistic studies of synthetic and biochemical reactions.<sup>4</sup> Hence, the syntheses of various chiral deuterated compounds through asymmetric reactions and the conversion from chiral pools have been reported by many groups.<sup>3</sup>

In contrast with well-known centrally chiral deuterated compounds, reports of isotopic atropisomerism due to the presence of deuterium atoms are very rare. In 1964 and 1972, Mislow and Bloch reported the synthesis of isotopically chiral biaryl compounds **III** and **IV** through the conversion from optically active precursors, whereas the optical rotation of **III** and **IV** was not detected because of the very slight difference between the *ortho*-CH<sub>3</sub> and CD<sub>3</sub> (CHD<sub>2</sub>) groups or the *meta*-H and -D atoms.<sup>5</sup> The creation of isotopically chiral atropisomers based on *ortho*-H/D discrimination should be more difficult than the creation of **III** and **IV** in terms of the rotational stability. That is, biaryl compound **VA** bearing an *ortho*-deuteriophenyl group will undergo quick racemization because the steric size of H and D atoms at the *ortho* position is too small for rotational restriction about a biaryl bond (Figure 1). Indeed, it was reported that even in biaryl **VB** bearing a fluorine atom, which is bulkier than a deuterium atom, racemization proceeds quickly at room temperature (rt).<sup>6</sup> In addition, the detection of isotopic atropisomerism is difficult. In centrally chiral compounds bearing H and D atoms on the same carbon such as **IA**, the stereochemistry and the optical purity were determined by NMR analysis after conversion to a diastereomeric derivative such as Mosher's ester (**IIA**).<sup>7</sup> On the contrary, the detection of chirality based on remote H and D atoms such as **VA** will not be easy.

In this Letter, we report the synthesis of diastereomeric 3-(2-deuteriophenyl)-2-(1-phenylpropan-2-yl)quinazoline-4-thione and the unprecedented isotopic atropisomerism (isotopic N–

C axial chirality **VI**, Figure 1) based on the *ortho*-H/D discrimination detected by NMR measurements.

In the course of our study on N–C axially chiral chemistry,<sup>8</sup> we found that 3-(2-fluorophenyl)-2-alkylquinazolin-4-one derivatives **VII** have a rotationally stable structure ( $\Delta G^\ddagger = 26.1\text{--}26.5\text{ kcal mol}^{-1}$ ), and their enantiomers can be separated at rt (half lives of racemization = 8.7–17 days at 298 K, Figure 2).<sup>9</sup> These are rare atropisomeric compounds with the smallest



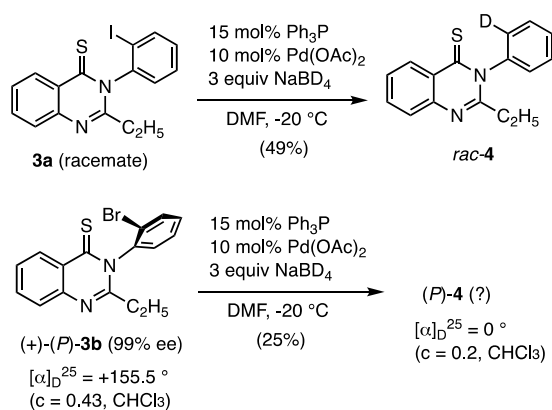
**Figure 2.** Rotational barriers around the N–Ar axis in several 3-aryl-2-alkylated quinazolin-4-ones.

hydrogen atom and the second smallest fluorine atom in the *ortho* position. The discovery of atropisomers based on *ortho*-H/F discrimination aroused our curiosity about creating isotopic atropisomers based on *ortho*-H/D discrimination.

The rotational barrier around the N–Ph axis in the phenyl analogue (3-phenyl-2-ethylquinazolin-4-one) **1** was explored in a density functional theory (DFT) study (B3LYP/cc-pVDZ in  $\text{CHCl}_3$ ) to verify the rotational stability of 4-quinazolinone bearing a 2-deuteriophenyl group.<sup>10</sup> The calculated barrier value ( $20.3\text{ kcal mol}^{-1}$ ) indicates that the N–Ph axis of **1** easily rotates at rt (half life of N–Ph bond rotation = 34 s at 298 K, Figure 2). Because the steric size of a deuterium atom is slightly smaller than that of a hydrogen atom,<sup>11</sup> 3-(2-deuteriophenyl)-2-ethylquinazolin-4-one was also predicted to be rotationally unstable. On the contrary, quite recently, we discovered that the conversion of N–C axially chiral quinazolinones to thione derivatives leads to a significant increase in the rotational barrier about an N–Ar chiral axis.<sup>12,13</sup> Indeed, the barrier value ( $24.1\text{ kcal mol}^{-1}$ ) of thione analogue **2** evaluated by DFT calculations was  $3.8\text{ kcal mol}^{-1}$  higher than that of **1**. The rotational stability of **2** (half life of N–Ph bond rotation = 5.5 h at 298 K) suggests that the physical isolation of enantiomers of the *ortho*-deuterio analogue is difficult by classical resolution methods, but the barrier is high enough to look for a separation of the enantiomers by chiral high-performance liquid chromatography (HPLC).

Racemic 3-(2-deuteriophenyl)-2-ethylquinazoline-4-thione *rac-4* was prepared through the reaction of 3-(2-iodophenyl)-2-ethylquinazoline-4-thione **3** with  $\text{NaBD}_4$  in the presence of a  $\text{Ph}_3\text{P}\text{--Pd}(\text{OAc})_2$  catalyst (Figure 3). The introduction of a deuterium atom was confirmed by comparing the high-resolution mass spectrometry (HRMS) and NMR spectra with N-phenyl derivative **2**. Subsequently, although the enantiomer separation of *rac-4* by HPLC using various chiral columns (AS, AD, OD, OJ, IA, IB N-5, IC, ID, IE, IF, IG, IH) and eluents (hexane, *i*-PrOH, AcOEt, tetrahydrofuran (THF),  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{Et}_2\text{NH}$ ) was attempted, no peak separation due to the enantiomers was observed.<sup>14</sup> This result may indicate that the column chiral selector could not discriminate the axial chirality based on the remote H and D atoms.

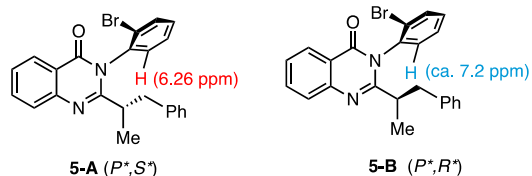
We also attempted the synthesis of optically active (*P*)-**4** from the optically pure *ortho*-bromophenyl derivative (+)-(*P*)-



**Figure 3.** Synthesis of 3-(2-deuteriophenyl)-2-ethylquinazoline-4-thione **4**.

**3b**, which was previously prepared by our group (Figure 3).<sup>12</sup> Unfortunately, optical rotation was not observed in the obtained deuterio derivative **4**. Thus the isotopic atropisomerism of the *ortho*-deuterated-phenyl derivative **4** could not be detected through the chiral HPLC method or optical rotation.

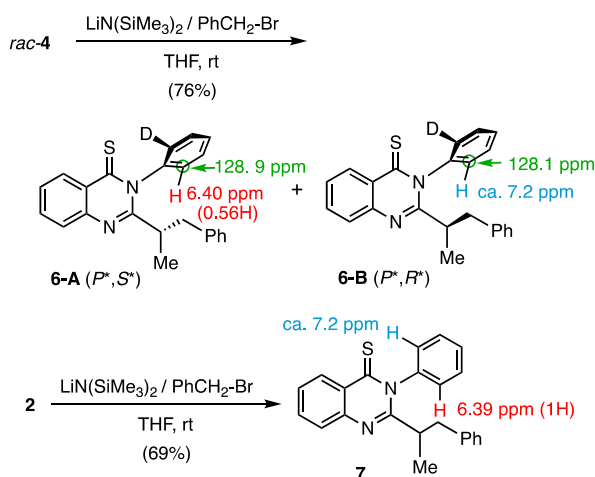
3-(2-Bromophenyl)-2-(1-phenylpropan-2-yl)quinazolin-4-one **5**, which is obtained through  $\alpha$ -benzylation of the enolate prepared from 3-(2-bromophenyl)-2-ethylquinazolin-4-one, presents two diastereomers based on an N–C axial chirality and a chiral carbon. In the  $^1\text{H}$  NMR spectra of **5**, the *ortho*-hydrogen in one diastereomer **5-A** possessing the (*P*\*,*S*\*) configuration appeared at a significantly higher magnetic field (6.26 ppm) than that (ca. 7.2 ppm) of another diastereomer **5-B** possessing the (*P*\*,*R*\*) configuration (Figure 4).<sup>15</sup> Because



**Figure 4.** Chemical shift of *ortho*-hydrogen in diastereomeric quinazolinone derivatives **5**.

the significant upfield shift of the *ortho*-hydrogen in one diastereomer was not observed in other  $\alpha$ -alkylation (allylation, ethylation, *iso*-propylation) products, this shift should be due to the anisotropic effect of the benzyl phenyl ring.

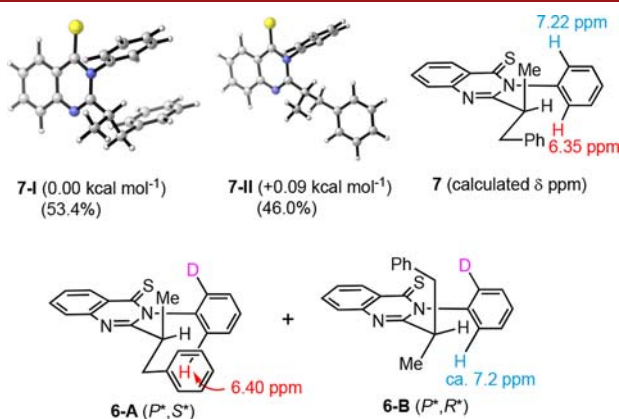
On the basis of the result depicted in Figure 4, we expected that the  $\alpha$ -benzylation of **4** would afford diastereomeric products and that isotopic atropisomerism may be detected in the signals of *ortho*-hydrogen atoms in the  $^1\text{H}$  NMR. The reaction of benzyl bromide with the enolate prepared from *rac-4* and  $\text{LiN}(\text{SiMe}_3)_2$  in THF gave the  $\alpha$ -benzylation product *rac-6* in 76% yield, and the  $^1\text{H}$  NMR of the obtained *rac-6* was compared with that of the N-phenyl analogue **7** (Figure 5). The  $^1\text{H}$  NMR chart of *rac-6* showed almost the same signals as **7**, and in both NMR charts, a significant difference was found in the chemical shift between *ortho*-hydrogen atoms (red and blue colors; 6.40 and ca. 7.2 ppm).<sup>16,17</sup> Meanwhile, the integrated value of *ortho*-hydrogen atoms in the *ortho*-deuterio derivative *rac-6* was about half of that in **7** (Figure 5). These results suggest that the signals of 6.40 and 7.2 ppm in the  $^1\text{H}$  NMR of *rac-6* are due to the *ortho*-hydrogen atoms of diastereomers (**6-A** and **6-B**) based on an N–C axial chirality



**Figure 5.** Synthesis of 3-(2-aryl)-2-(1-phenylpropan-2-yl)quinazoline-4-thiones **6** and **7** and the chemical shifts of  $^1\text{H}$  NMR in  $\text{CDCl}_3$  and  $^{13}\text{C}$  NMR in  $\text{CD}_2\text{Cl}_2$ .

and a chiral carbon, and *rac*-**6** exists as a 1:1 mixture of **6-A** and **6-B**. Furthermore, two kinds of *ortho*-CH (128.9 and 128.1 ppm) and *ortho*-CD (128.6 and 127.8 ppm) carbons, which were detected in  $^{13}\text{C}$  NMR, heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra, support the formation of **6-A** and **6-B**. (See the SI.)

The chemical shifts of *ortho*-hydrogen atoms in **6-A** and **6-B** were simulated by a computational study of the *N*-phenyl analogue **7** (Figure 6). That is, the structure of **7** in  $\text{CHCl}_3$  was

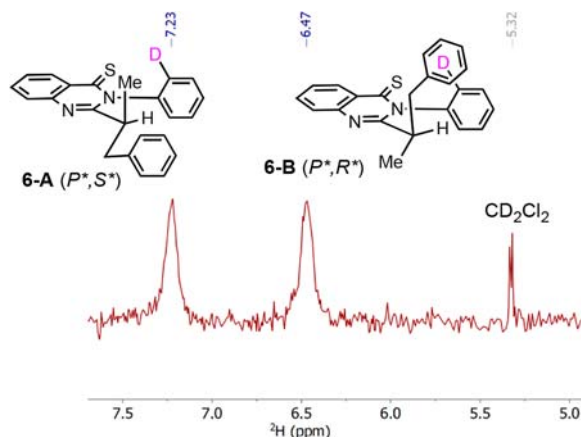


**Figure 6.** Stable conformers and the chemical shifts of *ortho*-hydrogen atoms in *N*-phenyl derivative **7** evaluated by DFT calculations (PBE1PBE/cc-pVDZ/ $\text{CHCl}_3$ (PCM)) and the preferential conformers of **6-A** and **6-B**.

evaluated by DFT calculations (PBE1PBE/cc-pVDZ), and two stable conformers **7-I** and **7-II** were found. (The relative energies of the other conformers were higher than 2.6 kcal  $\text{mol}^{-1}$  in comparison with those of **7-I** and **7-II**; see the SI.) The ratio of **7-I** and **7-II** is 53.4 and 46.0%, respectively, and **7-I** bearing Ph groups of face-to-face orientation causes an upfield shift of one *ortho*-hydrogen. That is, in conformer **7-I**, the *ortho*-hydrogen (red color) with  $\alpha$ -orientation (down-side) on the *N*-Ph group stands on the shielding cone of the benzyl phenyl ring, resulting in an upfield shift due to the anisotropic effect. On the contrary, another *ortho*-hydrogen (blue color) with  $\beta$ -orientation (up-side) is observed in the chemical shift

range of a “normal” aromatic hydrogen because it is located outside the influence of the benzyl phenyl ring. Because *ortho*-hydrogen in the deuterio phenyl derivative **6-A** is affected by benzyl phenyl ring, it should be detected at a much higher magnetic field than the *ortho*-hydrogen in another diastereomer **6-B** (Figure 6). Subsequently, the chemical shifts of two *ortho*-hydrogen atoms in **7** were predicted by using the gauge-independent atomic orbital (GIAO) method.<sup>18</sup> The hydrogen atoms of  $\alpha$ - and  $\beta$ -orientation were evaluated to appear at 6.35 and 7.22 ppm, respectively. These predicted chemical shift values are almost the same as those (6.40 and ca. 7.2 ppm) that were observed in  $^1\text{H}$  NMR of *rac*-**6** and **7** (Figure 5).<sup>16</sup> Thus signals of 6.40 and 7.2 ppm in the  $^1\text{H}$  NMR of *rac*-**6** were assigned to the *ortho*-hydrogen atoms in diastereomers **6-A** ( $P^*, S^*$ ) and **6-B** ( $P^*, R^*$ ), respectively (Figure 6).

The occurrence of diastereomers **6-A** and **6-B** was also verified by a  $^2\text{H}$  NMR measurement. In the  $^2\text{H}$  NMR of *rac*-**6** in  $\text{CH}_2\text{Cl}_2$ , two deuterium signals were observed at 6.47 and 7.23 ppm, respectively (Figure 7). Their chemical shifts are



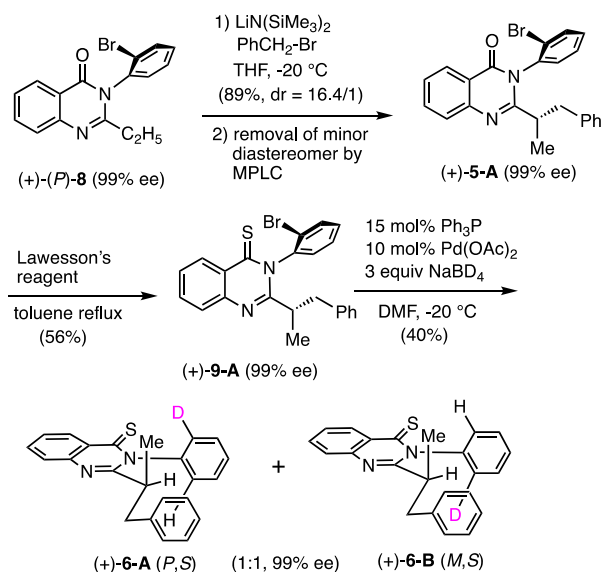
**Figure 7.**  $^2\text{H}$  NMR spectrum of **6** in  $\text{CH}_2\text{Cl}_2$ .

similar to those (6.38 and 7.2 ppm) of *ortho*-hydrogen atoms in  $^1\text{H}$  NMR, and signals of 6.47 and 7.23 ppm were assigned to the deuterium of **6-B** and **6-A**, respectively. (The deuterium in **6-B** was observed at a higher magnetic field because of the anisotropic effect of the benzyl phenyl ring.)

Thus  $^1\text{H}$ ,  $^2\text{H}$ , and  $^{13}\text{C}$  NMR spectra strongly support the formation of an isotopic atropisomer due to the rotational restriction around the *N*-(2- $\text{D}$ ) $\text{C}_6\text{H}_4$  bond in *rac*-**6**. Furthermore, the synthesis of the optically active deuterio compound (+)-**6** was attempted (Scheme 1). The highly diastereoselective  $\alpha$ -benzylation with (+)-(*P*)-**8** (99% ee) was followed by the removal of the minor diastereomer through medium-pressure liquid chromatography (MPLC), affording the stereochemically pure (+)-**5-A** possessing the (*P,S*) configuration in a good yield.<sup>15</sup> (+)-**5-A** was converted to thione (+)-**9-A** without any epimerization or racemization through the reaction with Lawesson's reagent.

We attempted the selective synthesis of diastereomer (+)-**6-A** via the deuteration of (+)-**9-A** with  $\text{NaBD}_4$ . Although the workup and NMR measurements were conducted as quickly as possible, the preferential formation of (+)-**6-A** could not be ascertained. In this case, the epimerization of the (*P,S*)-isomer (+)-**6-A** into the (*M,S*)-isomer (+)-**6-B** occurs quickly, resulting in a 1:1 mixture of the two optically pure diastereomers (+)-**6-A** and (+)-**6-B**. On the contrary, the

**Scheme 1. Synthesis of Optically Active 3-(2-Deuteriophenyl)-2-(1-phenylpropan-2-yl)quinazoline-4-thione 6**



variable temperature (VT)-NMR of **6** was measured at 300–350 K in deuterated tetrachloroethane; however, neither the coalescence of signals nor the signal broadening was observed. The rotational barrier around the N–Ar axis in the Ph analogue **7** was evaluated to be  $23.7\text{ kcal mol}^{-1}$  ( $t_{1/2} = 3.1\text{ h}$  at 298 K) by DFT calculations (B3LYP/cc-pVDZ/ $\text{CHCl}_3(\text{PCM})$ ).

In conclusion, we prepared diastereomeric 3-(2-deuteriophenyl)-2-(1-phenylpropan-2-yl)quinazoline-4-thione and detected isotopic atropisomerism owing to the rotational restriction around the N–Ar axis based on the NMR spectra. Although the present atropisomerism was not stable (class 2 atropisomers) because of the extremely small steric size of the hydrogen and deuterium atoms, as far as we know, this work is the first time a class 2 isotopic atropisomer based on *ortho*-H/D discrimination has been detected.<sup>19</sup> In addition, because *N*-aryl quinazolinones and the thione analogues are pharmaceutically attractive compounds, this result is also of great interest from the viewpoint of medicinal chemistry.

(1) For representative reviews: (a) Mutlib, A. E. Application of Stable Isotope-Labeled Compounds in Metabolism and in Metabolism-Mediated Toxicity Studies. *Chem. Res. Toxicol.* **2008**, *21*, 1672–1689. (b) Gómez-Gallego, M.; Sierra, M. A. Kinetic Isotope Effects in the Study of Organometallic Reaction Mechanisms. *Chem. Rev.* **2011**, *111*, 4857–4963. (c) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072. (d) Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid, M. Deuterium- and Tritium-Labelled Compounds: Applications in the Life Sciences. *Angew. Chem., Int. Ed.* **2018**, *57*, 1758–1784.

(2) For recent reviews, see: (a) Harbeson, S. L.; Tung, R. D. Deuterium Medicinal Chemistry: A New Approach to Drug Discovery and Development. *MEDCHEM NEWS* **2014**, *24*, 8–22. (b) Gant, T. G. Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem.* **2014**, *57*, 3595–3611. (c) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 5276–5297.

(3) For representative papers, see: (a) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. Chiral trialkylborane reducing agents: Preparation of 1-deuterio primary alcohols of high enantiomeric purity. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355. (b) Nishizawa, M.; Noyori, R. Asymmetric synthesis of chiral geraniol-1-d and related terpenic alcohols. *Tetrahedron Lett.* **1980**, *21*, 2821–2824. (c) Harris, R. N., III; Sundararaman, P.; Djerassi, C. Optical rotatory dispersion studies. 135. Synthesis and chiroptical properties of (S)- and (R)- $(3\text{-}^2\text{H}_1)\text{-2,2-dimethylcyclobutanone}$ . Evidence for conformational effects in substituted cyclobutanones. *J. Am. Chem. Soc.* **1983**, *105*, 2408–2413. (d) Corey, E. J.; Link, J. O. A new chiral catalyst for the enantioselective synthesis of secondary alcohols and deuterated primary alcohols by carbonyl reduction. *Tetrahedron Lett.* **1989**, *30*, 6275–6278. (e) Bradshaw, C. W.; Lalonde, J. J.; Wong, C. Enzymatic synthesis of (R)- and (S)-1-deuteriohexanol. *Appl. Biochem. Biotechnol.* **1992**, *33*, 15–24. (f) Kimata, K.; Kobayashi, M.; Hosoya, K.; Araki, T.; Tanaka, N. Chromatographic Separation Based on Isotopic Chirality. *J. Am. Chem. Soc.* **1996**, *118*, 759–762. (g) Haesler, J.; Schindelholz, I.; Riguet, E.; Bochet, C. G.; Hug, W. *Nature* **2007**, *446*, 526–529. (h) Chen, Y.; Tang, W.-L.; Mou, J.; Li, Z. High-Throughput Method for Determining the Enantioselectivity of



- Enzyme-Catalyzed Hydroxylations Based on Mass Spectrometry. *Angew. Chem., Int. Ed.* **2010**, *49*, 5278–5283. (i) Herwig, P.; Zawatzky, K.; Grieser, M.; Heber, O.; Jordon-Thaden, B.; Krantz, C.; Novotny, O.; Repnow, R.; Schurig, V.; Schwalm, D.; Vager, Z.; Wolf, A.; Trapp, O.; Kreckel, H. Imaging the absolute configuration of a chiral epoxide in the gas phase. *Science* **2013**, *342*, 1084–1086. (j) Masarwa, A.; Gerbig, D.; Oskar, L.; Loewenstein, A.; Reisenauer, H. P.; Lesot, P.; Schreiner, P. R.; Marek, I. Synthesis and Stereochemical Assignment of Crypto-Optically Active  $^2\text{H}_6$ -Neopentane. *Angew. Chem., Int. Ed.* **2015**, *54*, 13106–13109.
- (4) (a) Holland, H. L.; Brown, F. M.; Munoz, B.; Ninniss, R. W. Side chain hydroxylation of aromatic hydrocarbons by fungi. Part 2. Isotope effects and mechanism. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1557–1563. (b) Yamamoto, T.; Tokunaga, E.; Nakamura, S.; Shibata, N.; Toru, T. Synthesis and Configuration Stability of (S)- and (R)-Deuteriothalidomides. *Chem. Pharm. Bull.* **2010**, *58*, 110–112. (c) Kawasaki, T.; Ozawa, H.; Ito, M.; Soai, K. Enantioselective Synthesis Induced by Compounds with Chirality Arising from Partially Deuterated Methyl Groups in Conjunction with Asymmetric Autocatalysis. *Chem. Lett.* **2011**, *40*, 320–321. (d) Liu, W.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. Probing the C-O Bond-Formation Step in Metalloporphyrin-Catalyzed C-H Oxygenation Reactions. *ACS Catal.* **2017**, *7*, 4182–4188.
- (5) (a) Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, H., Jr. Conformational Kinetic Isotope Effects in the Racemization of 9,10-Dihydro-4,5-dimethylphenanthrene. *J. Am. Chem. Soc.* **1964**, *86*, 1733–1741. (b) Bloch, M.; Lau, N.; Musso, H.; Zahorszky, U. I. (S)-Bimesityl-3,3-d $_2$ . *Chem. Ber.* **1972**, *105*, 1790–1797.
- (6) Koshino, S.; Takikawa, A.; Ishida, K.; Taniguchi, T.; Monde, K.; Kwon, E.; Umemiya, S.; Hayashi, Y. Inversion of the Axial Information during Oxidative Aromatization in the Synthesis of Axially Chiral Biaryls with Organocatalysis as a Key Step. *Chem. - Eur. J.* **2020**, *26*, 4524–4530.
- (7) (a) Sato, I.; Omiya, D.; Saito, T.; Soai, K. Highly Enantioselective Synthesis Induced by Chiral Primary Alcohols Due to Deuterium Substitution. *J. Am. Chem. Soc.* **2000**, *122*, 11739–11740. (b) Balkenende, D. W. R.; Cantekin, S.; Duxbury, C. J.; van Genderen, M. H. P.; Meijer, E. W.; Palmans, A. R. A. Enantioselective Synthesis of (R)- and (S)-1- $^2\text{H}$ -1-Octanol and Their Corresponding Amines. *Synth. Commun.* **2012**, *42*, 563–573. (c) Küppers, J.; Rabus, R.; Wilkes, H.; Christoffers, J. Optically Active 1-Deuterio-1-phenylethane – Preparation and Proof of Enantiopurity. *Eur. J. Org. Chem.* **2019**, *2019*, 2629–2634.
- (8) Kitagawa, O. Chiral Pd-Catalyzed Enantioselective Syntheses of Various N-C Axially Chiral Compounds and Their Synthetic Application. *Acc. Chem. Res.* **2021**, *54*, 719–730.
- (9) (a) Iida, A.; Matsuoka, M.; Hasegawa, H.; Vanthuyne, N.; Farran, D.; Roussel, C.; Kitagawa, O. N-C Axially Chiral Compounds with an *ortho*-Fluoro Substituents and Steric Discrimination between Hydrogen and Fluorine Atoms Based on a Diastereoselective Model Reaction. *J. Org. Chem.* **2019**, *84*, 3169–3175. (b) Iida, A.; Saito, K.; Asada, N.; Fujimoto, Y.; Kitagawa, O. Study on Rotational Stability of 2-Aryl-3-(2-Fluorophenyl)Quinazolin-4-One Derivatives. *Heterocycles* **2021**, *103*, 183–189.
- (10) The calculations for the rotational barrier were conducted as follows: The relaxed scan about the rotation of the N–Ar axis under the B3LYP/6-31+G(d) level of theory provided the potential energy surface (PES) for the rotational barrier; then, we sought the saddle point from the energetically highest geometry on the obtained PES. The transition-state optimization and the vibrational calculation were performed under the B3LYP/cc-pVDZ level of theory. In addition, the rotational barriers of compounds **1**, **2**, and **7** in  $\text{CHCl}_3$  were calculated because in compounds **VII**, there was a good correlation between the experimental and calculated barrier values in  $\text{CHCl}_3$ .
- (11) (a) Melander, L.; Carter, R. E.; Asen, S.; Halvarson, H.; Nilsson, L. The Deuterium Isotope Effect in the Racemization of 2,2'-Dibromo-4,4'-Dicarboxybiphenyl. *Acta Chem. Scand.* **1964**, *18*, 1138–1149. (b) Melander, L.; Carter, R. E. Steric Isotope Effect. Isotope Effect on the Racemization of 2,2'-Dibromo-4,4'-Dicarboxybiphenyl. *J. Am. Chem. Soc.* **1964**, *86*, 295–296.
- (12) Nijijima, E.; Imai, T.; Suzuki, H.; Fujimoto, Y.; Kitagawa, O. Thionation of Optically Pure N-C Axially Chiral Quinazolin-4-one Derivatives with Lawesson's Reagent. *J. Org. Chem.* **2021**, *86*, 709–715.
- (13) The increase in the rotational barriers about an N–C axis by the conversion to thioamide derivatives has also been found by several groups: (a) Roussel, C.; Stein, J. L.; Beauvais, F. Separation of Atropisomers on CSP Microcrystalline Cellulose Triacetate and Barriers to Rotation in Some Polymethyl-3-phenyl-D-4-thiazolin-2-thiones and Their Oxygen Analogs. *New J. Chem.* **1990**, *14*, 169. (b) Sarac-Arneri, R.; Mintas, M.; Pustet, N.; Mannschreck, A. Syntheses, Separation of Enantiomers and Barriers to Racemization of Some Sterically Hindered N-Aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones and Their Thio Analogues. *Monatsh. Chem.* **1994**, *125*, 457. (c) Yilmaz, E. M.; Dogan, I. Axially Chiral N-(*o*-Aryl)-2-thioxo-oxazolin-4-one and Rhodanine Derivatives: Enantiomer Separation and Determination of Racemization Barriers. *Tetrahedron: Asymmetry* **2008**, *19*, 2184. (d) Zhang, J.; Liu, Z.; Yin, Z.; Yang, X.; Ma, Y.; Szostak, R.; Szostak, M. Preference of cis-Thioamide Structure in N-Thioacyl-N-methylanilines. *Org. Lett.* **2020**, *22*, 9500–9505. (e) Li, G.; Ma, S.; Szostak, M. Amide Bond Activation: The Power of Resonance. *Trends Chem.* **2020**, *2*, 914–928.
- (14) In a few centrally chiral deuterated compounds, the chromatographic separation of enantiomers using a chiral stationary phased was reported: Pirkle, W. H.; Gan, K. Z. A direct chromatographic separation of enantiomers chiral by virtue of isotopic substitution. *Tetrahedron: Asymmetry* **1997**, *8*, 811–814. See also ref **3c**.
- (15) Matsuoka, M.; Goto, M.; Wzorek, A.; Soloshonok, V. A.; Kitagawa, O. Diastereoselective  $\alpha$ -Alkylation of Metallo Enamines Generated from N-C axially Chiral Mebroqualone Derivatives. *Org. Lett.* **2017**, *19*, 2650–2653.
- (16) The exact chemical shift and integrated value of the *ortho*-hydrogen (blue color) in **6-B** and **7** were not described because of the overlap with the signals of other aromatic hydrogen atoms.
- (17) The NMR signals of all hydrogen atoms and carbon atoms in deuterio derivatives **4** and **6** were assigned through HSQC and HMBC. (See the **SI**.)
- (18) All calculations were carried out by using the Gaussian 09 program (rev. D.01), and we used the gauge-independent atomic orbital (GIAO) method for the NMR chemical shift predictions. (See the **SI**.)
- (19) Fan and Kagan et al. succeeded in the detection of atropisomerism in a biaryl compound bearing an *ortho*-deuterio phenyl group [1-(2-deuterio-4-methylphenyl)naphthalene] by a  $^2\text{H}$  NMR measurement in chiral liquid crystals while the rotational barriers about the biaryl bond were very low (11.6 kcal mol $^{-1}$ , class 1 atropisomers): Lafon, O.; Lesot, P.; Fan, C.-A.; Kagan, H. B. Analysis of Intramolecular Dynamic Processes in Enantiomeric Diaryl Atropisomers and Related Derivatives by  $^2\text{H}$  NMR Spectroscopy in Polypeptide Liquid Crystals. *Chem. - Eur. J.* **2007**, *13*, 3772–3786.