

# Atropisomeric Racemization Kinetics of MRTX1719 Using Chiral Solvating Agent-Assisted $^{19}\text{F}$ NMR Spectroscopy

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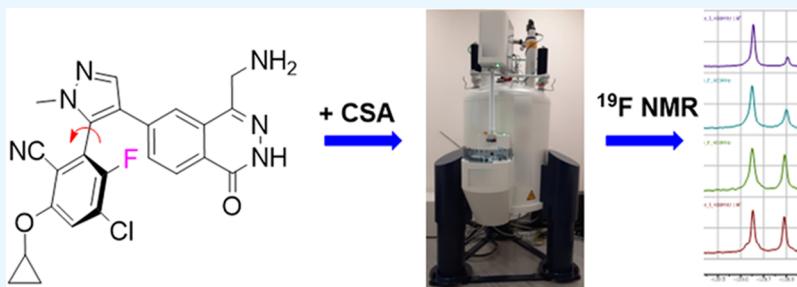
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**ABSTRACT:** With renewed interest in atropisomerism of drug molecules, efficient methods to experimentally determine torsion rotational energy barriers are needed. Here, we describe use of the chiral phosphoric acid solvating agent (+)-TiPSY to resolve the signals of atropisomers in  $^{19}\text{F}$  NMR and to use the data to study the kinetics of racemization and determine the rotational energy barrier of clinical compound **MRTX1719**. This method is complimentary to traditional chiral high-performance liquid chromatography (HPLC) and enhances the toolkit for chiral analysis techniques.

## 1. INTRODUCTION

**MRTX1719**, an inhibitor of the PRMT5-MTA complex, was recently disclosed<sup>1</sup> and is in a phase 1/2 clinical study in solid tumors with *MTAP* deletions. One of the distinct structural characteristics of **MRTX1719** is the axis of chirality along the C–C bond connecting the pentasubstituted phenyl to the methyl pyrazole group (red arrow, Scheme 1). The calculated torsion rotational energy barrier ( $\Delta E_{\text{rot}}$ ) for **MRTX1719** was found<sup>2</sup> to be  $\Delta E_{\text{rot}} = 31.5$  kcal/mol. LaPlante et al. disclosed a classification system for atropisomers using the calculated  $\Delta E_{\text{rot}}$  of rotation, and according to this system, **MRTX1719** is a class 3 atropisomer.<sup>3</sup> Class 3 atropisomers are characterized by slow rotation along the C–C bond with interconversion half-life measured in years. Here, we disclose a method to measure the experimental barrier of rotation in solution of the atropisomeric C–C bond in **MRTX1719** using  $^{19}\text{F}$  NMR in the presence of a chiral solvating agent (CSA).

Atropisomerism as a structural feature has attracted significant attention in the drug discovery community in recent years.<sup>4,5</sup> Currently, only a handful of food and drug administration (FDA)-approved drugs are atropisomERICALLY stable compounds. Three were approved as mixtures of atropisomers, telenzepine,<sup>6</sup> colchicine,<sup>7</sup> and lesinurad,<sup>8</sup> while sotorasib<sup>9</sup> was recently approved as a single atropisomer, shown in Figure 1a. In addition, multiple single atropisomeric compounds have been described at various stages of preclinical and clinical development, see Figure 1b for three examples.<sup>10–12</sup>

Developing a drug as a single stable atropisomer as opposed to a racemic mixture can offer certain advantages such as enhanced potency and a simplified regulatory path to approval. Indeed, in a cell proliferation assay (−)-**MRTX1719** is almost 300 times more potent than its corresponding distomer (+)-**MRTX1719** (Scheme 1). In addition, there are synthetic and analytical challenges specific to developing drugs as single atropisomers, for example, the need for an enantioselective synthesis or a potentially costly and time-consuming chiral separation, as well as the need to develop robust analytical methods to assess enantiopurity and to study racemization rates and stability.

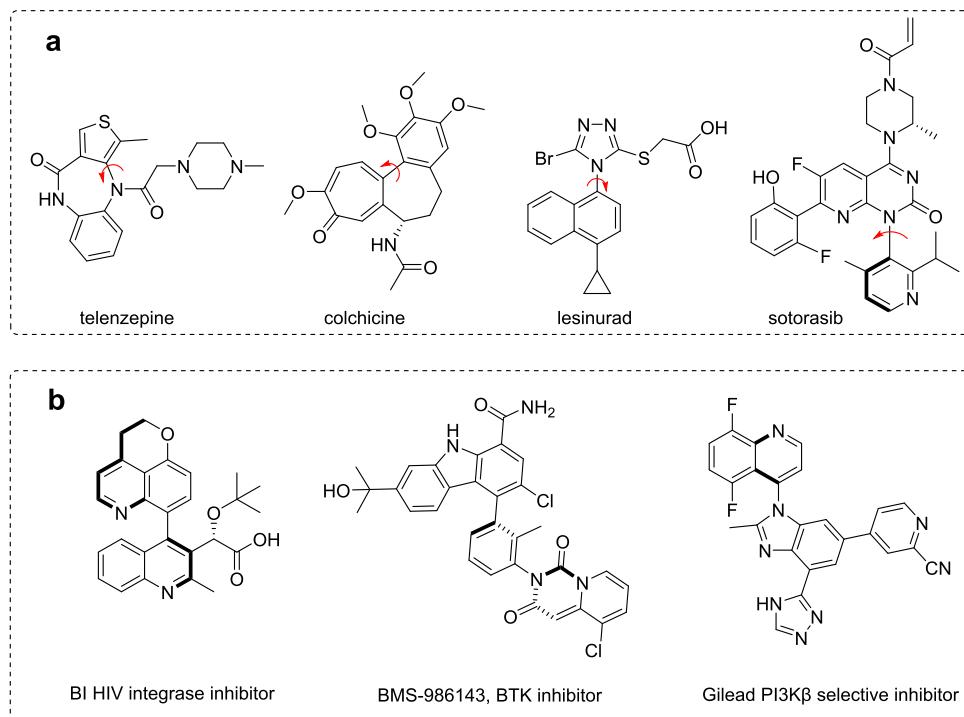
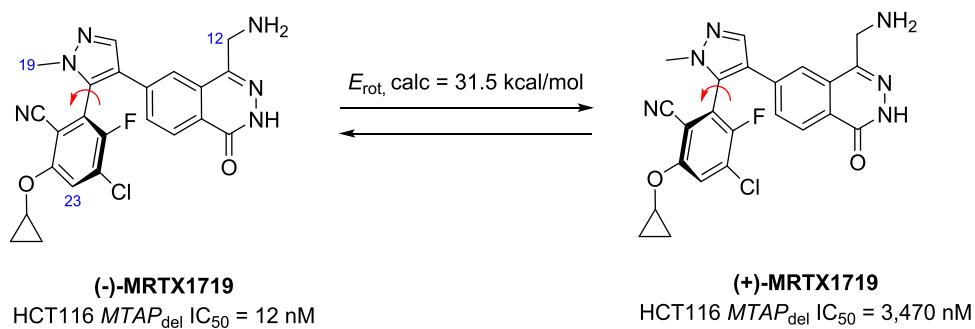
High-performance liquid chromatography (HPLC) and supercritical fluid chromatography (SFC) are by far the most popular analytical methods to determine the enantiopurity of chiral molecules. While quick and convenient for established systems, using these methods for novel compounds can involve extensive condition screening and requires scouting runs across a number of chiral stationary phases. One disadvantage that we experienced with HPLC and SFC methods was that for some analogs, we could not definitively determine the atropisomeric

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**Scheme 1.** Structure of MRTX1719 and Its Distomer**Figure 1.** (a) FDA-approved atropisomeric compounds; (b) examples of single atropisomers from medicinal chemistry literature.

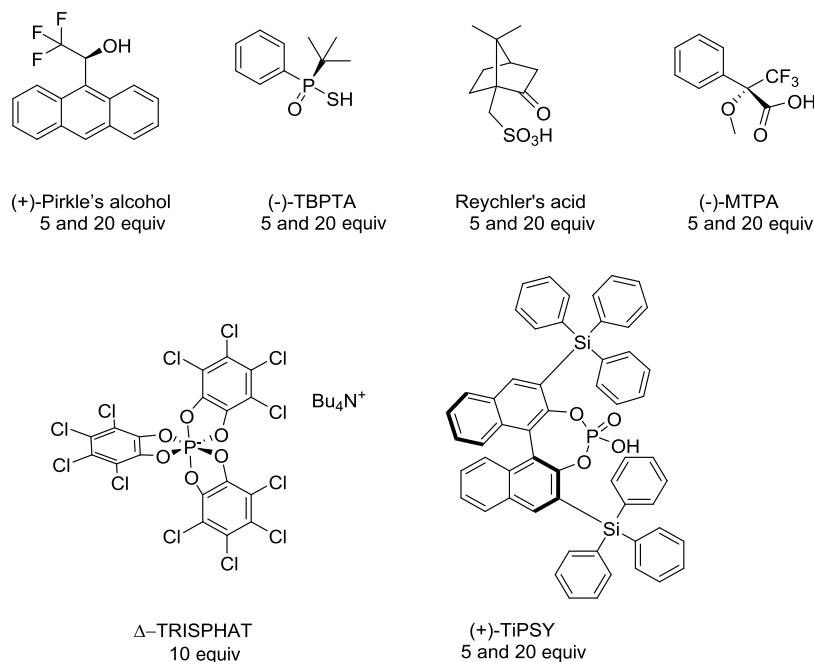
properties of the compounds of interest. For example, we could not ascertain if a lack of separation after screening approximately 70 HPLC or SFC conditions was due to the atropisomeric properties of the compound (i.e., fast interconversion of atropisomers) or due to an inability to find an appropriate HPLC or SFC method of separation.<sup>1</sup> Additionally, an excessive cost is often associated with the equipment, including chiral columns and the frequent need for long run times.

Another widely used technique to determine enantiopurity is NMR. One approach relies on derivatization of a chiral test article with a chiral derivatizing agent followed by <sup>1</sup>H NMR analysis to determine the enantiomeric excess via the analysis of the diastereoisomeric mixture. Mosher esters and amides are important textbook examples illustrating the use of chiral derivatizing agents.<sup>13</sup> Limitations of the derivatization method include the need for the test compound to contain a functional group suitable for derivatization and for the stereoisomer to be inert to racemization under the derivatization conditions. In this regard, noncovalent approaches to eliminate enantiomer isochrony by transferring enantiomers into a diastereomeric environment in the presence of CSAs or chiral lanthanide shift

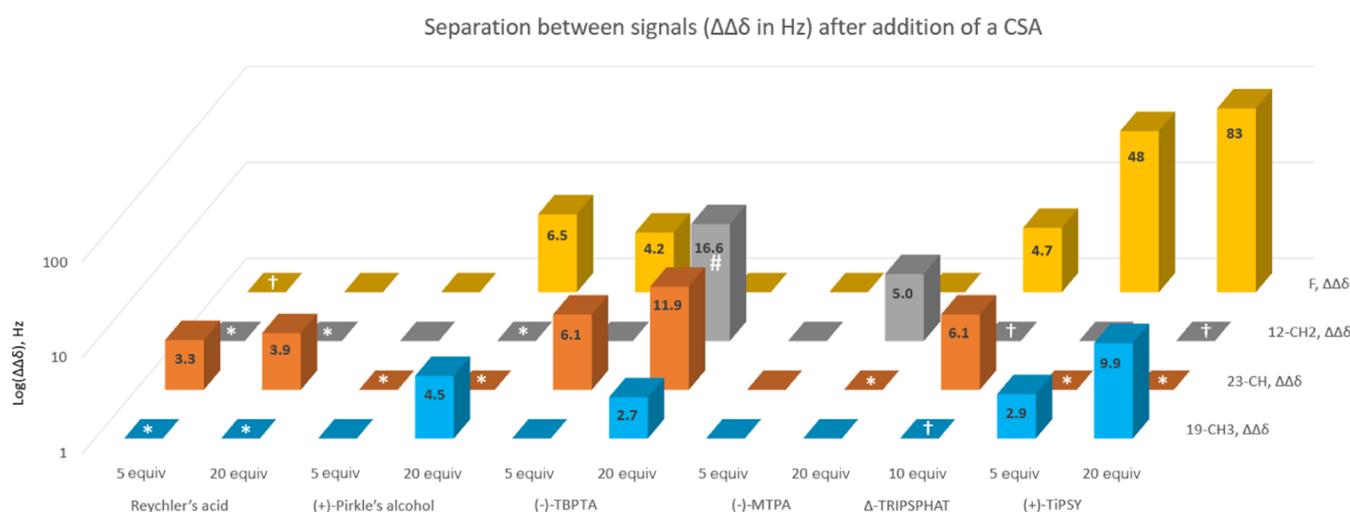
reagents present a more attractive alternative.<sup>14,15</sup> Therefore, we focused on examining CSAs to develop an NMR-based analytical technique to characterize the racemization kinetics of MRTX1719. Recently, Jiang et al.<sup>16</sup> described the use of chiral phosphoric acid CSAs and <sup>1</sup>H NMR to determine the enantiopurity of a set of atropisomeric quinolines. The method described herein capitalizes on the presence of a fluorine atom in the studied molecule and can potentially be extended to study racemization kinetics of other fluorine-containing chiral molecules. While similar analytical chiral <sup>19</sup>F NMR methods have been described for various classes of compounds,<sup>17–20</sup> reported examples using <sup>19</sup>F NMR and CSAs to determine the rate of racemization are limited.<sup>21</sup>

## 2. RESULTS AND DISCUSSION

We initially screened the racemate of MRTX1719 with several CSAs to identify the most suitable system for resolving distinct resonances in the <sup>1</sup>H and/or <sup>19</sup>F NMR spectra. Figure 2 depicts the structures and the equivalents of the CSAs used in screening. A set of mostly acidic CSAs was chosen due to the basic nature of MRTX1719 (primary benzylamine conjugate acid  $pK_a = 8$ ). Nonequivalent values of racemic free base



**Figure 2.** CSA structures and equivalents relative to MRTX1719.



**Figure 3.** CSA-induced separation of signals in <sup>1</sup>H and <sup>19</sup>F NMR spectra. The numbers in the bars represent  $\Delta\Delta\delta$  in linear scale in Hz. \*Resonance obscured by CSA or residual water peaks. †Resonance(s) of MRTX1719 broad. #Only de-shielded doublet observed cleanly.

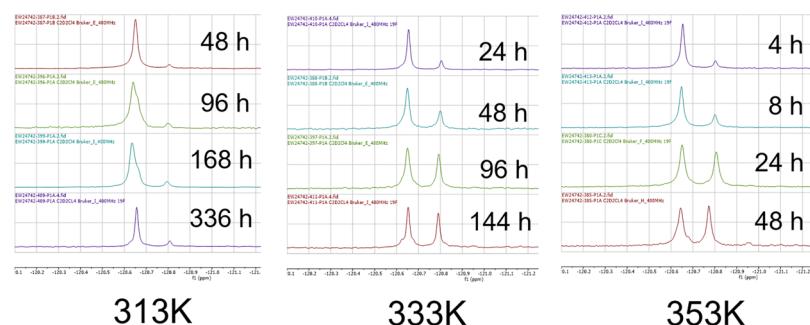
**MRTX1719** <sup>1</sup>H and <sup>19</sup>F NMR peaks with a range of CSAs in *D*<sub>2</sub>-tetrachloroethane (*D*<sub>2</sub>-TCE) solution are summarized in Figure 3.

In the <sup>1</sup>H NMR spectra, there was a noticeable separation of the 23-CH signal as two overlapping doublets in the presence of 10 equiv of  $\Delta$ -TRISPHAT, 5 or 20 equiv of (-)-TBPTA, and 20 equiv of Reychler's acid. 20 equiv of (-)-TBPTA also provided separation of peaks 12-CH<sub>2</sub> and 19-CH<sub>3</sub>. (+)-Pirkle's alcohol, (-)-MTPA, and (+)-TiPSY displayed overlapping aromatic signals with racemic MRTX1719 in the 23-CH region. However, (+)-Pirkle's alcohol, (-)-MTPA, and (+)-TiPSY demonstrated appreciable differences in their effect on the separation of 12-CH<sub>2</sub> or 19-CH<sub>3</sub> between 5 and 20 equiv of CSA.

In the <sup>19</sup>F NMR spectra, addition of 5 or 20 equiv of (-)-MTPA or 5 equiv of (+)-Pirkle's alcohol had no effect on the fluorine signal. Typically, 10 equiv of  $\Delta$ -TRISPHAT and

20 equiv of (+)-Pirkle's alcohol led to slight splitting. In the case of (-)-TBPTA, the <sup>19</sup>F NMR data were ambiguous, for there was an apparent difference with 5 equiv but no difference observed with 20 equiv. (+)-TiPSY gave the most encouraging results with clear, concentration-dependent separation of the peaks observed (5 equiv  $\Delta\Delta\delta$  = 48 Hz and 20 equiv  $\Delta\Delta\delta$  = 83 Hz in <sup>19</sup>F NMR acquired at 376.6 MHz). Unlike the overlapping multiplets of aromatic protons observed in the <sup>1</sup>H NMR spectra, the fluorine singlet peak in the <sup>19</sup>F NMR spectra was cleanly split and well resolved at the baseline in the presence of the CSA. This high resolution facilitated by the large dynamic range of <sup>19</sup>F NMR enabled a more precise integration of the peaks compared to <sup>1</sup>H NMR, thereby providing a more precise quantification of the species.

Encouraged by the clear separation of signals in the <sup>19</sup>F NMR spectra produced by the (+)-TiPSY CSA, we conducted further validation studies, including method reproducibility



**Figure 4.**  $^{19}\text{F}\{^1\text{H}\}$  NMR spectra of ( $-$ )-MRTX1719 free base in  $\text{D}_2\text{-TCE}$  with 20 equiv of (+)-TiPSY CSA after heating at 313, 333, and 353 K and collecting the data at the indicated time points.

studies. It was determined that 20 equiv of (+)-TiPSY gave the best peak separation and reproducibility. The finalized design of the racemization kinetics study involved heating a solution of MRTX1719 in an NMR tube; then, at the desired time point, the sample was cooled to room temperature, 20 equiv of (+)-TiPSY was added, and the  $^{19}\text{F}$  NMR spectra were collected.

The racemization study was carried out with the recrystallized enantiomer of ( $-$ )-MRTX1719 (free base) at three temperatures and four time points per temperature. After the defined heating period in  $\text{D}_2\text{-TCE}$ , the samples were cooled and analyzed by  $^{19}\text{F}$  NMR with  $^1\text{H}$  decoupling in the presence of 20 equiv of (+)-TiPSY. The resulting spectra are illustrated in Figure 4, and the percentage peak areas are summarized in Table 1.

**Table 1. Summary of  $^{19}\text{F}\{^1\text{H}\}$  NMR Data**

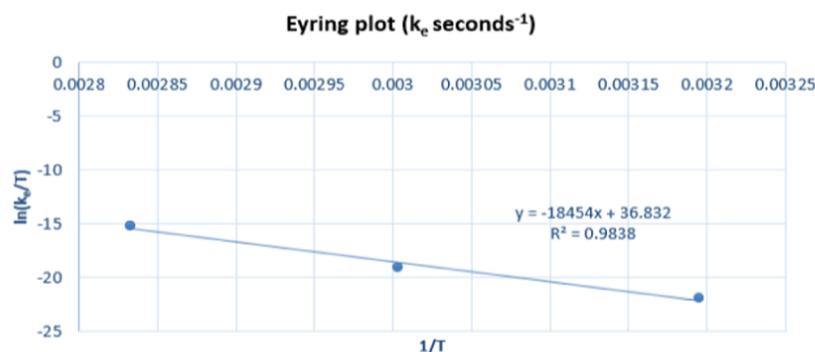
temp. (K)	time (h)	%A <sup>a</sup>	%B <sup>b</sup>	%ee <sup>c</sup>	$k_{\text{rac}}$ ( $\text{h}^{-1}$ ) <sup>d</sup>
313	48	93.80	6.20	87.6	0.0007
	96	96.70	3.30	93.4	
	168	93.10	6.90	86.2	
	336	86.90	13.10	73.8	
333	24	83.30	16.70	66.6	0.0124
	48	69.20	30.80	38.4	
	96	60.80	39.20	21.6	
	144	57.10	42.90	14.2	
353	4 <sup>e</sup>	85.20	14.80	70.4	0.6481
	8 <sup>e</sup>	76.20	23.80	52.4	
	24	57.00	43.00	14.0	
	48	56.30	43.70	12.6	

<sup>a</sup>A = starting material. <sup>b</sup>B = enantiomer of A. <sup>c</sup>Enantiomeric excess.

<sup>d</sup>Racemization constant. <sup>e</sup>Spectrum acquired with  $d_1 = 1$ .

Racemization constants were determined for each temperature by tracking percentage enantiomeric excess (%ee) decay over time (Table 1, also see the Supporting Information). The solution half-lives were found to be 990 h at 313 K, 56 h at 333 K, and 1 h at 353 K. To our satisfaction, when extrapolated from the Eyring plot (Figure 5), the half-life of MRTX1719 at room temperature (298 K) in solution was calculated to be 2.9 years. The Gibbs free energy barrier ( $\Delta G^\ddagger$  at 25 °C)<sup>22</sup> for the rotation around the axial chirality bearing C–C bond was found to be 28.93 kcal/mol.

To validate this result, we utilized a traditional chromatographic method to determine the barrier of rotation. Two alternative salt forms and solvents were utilized to account for any potential sensitivity to the matrix. The samples were analyzed by a chiral normal phase (NP) HPLC method. For the hydrochloride form of MRTX1719, heating of the samples was carried out in 2 M HCl in methanol to mimic potential API manufacturing conditions. According to the experimental design for this study, 5–6 time points were collected at four equilibration temperatures (30–60 °C in 10 °C increments). For the free base form of MRTX1719, heating of the samples was carried out in dimethyl sulfoxide (DMSO), and at the selected time points, the spectra were collected from the equilibrated samples at 6 temperatures (50–100 °C in 10 °C increments) (see the Supporting Information). The Eyring plot data from the  $^{19}\text{F}$  NMR study and two HPLC studies are summarized in Table 2. To our delight, all three methods gave remarkably similar  $\Delta G^\ddagger$  (or  $\Delta E_{\text{rot}}$ ) values, with a standard deviation <0.2 kcal/mol. MRTX1719 as a free base in DMSO measured by chiral NP HPLC and in  $\text{D}_2\text{-TCE}$  measured by  $^{19}\text{F}$  NMR were the closest, at 28.90 and 28.93 kcal/mol, respectively. Kinetic measurements for the hydrochloride in methanolic HCl solution resulted in the slightly lower barrier



**Figure 5.** Eyring plot for the  $^{19}\text{F}$  NMR study.

**Table 2.** Comparison of MRTX1719 Racemization Energetics Using Three Methods

method	MRTX1719 form	solvent	slope	intercept	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (kcal/mol·K)	$\Delta G^\ddagger$ at 25 °C (kcal/mol)
<sup>19</sup> F NMR	free base	TCE	-18 454	36.832	36.67	0.0260	28.93
NP HPLC	free base	DMSO	-13 399	19.914	26.62	-0.00764	28.90
NP HPLC	HCl	MeOH	-14 914	25.549	29.63	0.00355	28.57

of rotation at 28.57 kcal/mol, still very well aligned with the other data.

According to LaPlante et al.,<sup>3</sup> the rotation barrier of  $\Delta G^\ddagger$  (25 °C) at 28.93 kcal/mol in solution places MRTX1719 at the interface between class 2 and class 3 atropisomers. However, with the racemization half-life determined at 2.9 years (298 K), we concluded MRTX1719 is suitably stable for pharmaceutical development. In addition, the undesired atropisomer (+)-MRTX1719 can be racemized by heating in an alcoholic solution at 70–80 °C for 48–72 h, allowing recycling of the undesired isomer and consequently improving the efficiency of the synthesis.

### 3. CONCLUSIONS

The rotation barrier for MRTX1719 was determined using <sup>19</sup>F NMR in the presence of chiral solvating agent (+)-TiPSY. The resulting  $\Delta G^\ddagger$  at 25 °C = 28.93 kcal/mol is in good agreement with the calculated value (31.5 kcal/mol) and is very well aligned with data obtained using chromatographic techniques. The <sup>19</sup>F NMR kinetics study described here offers a viable alternative to conventional methods and can be an attractive option utilizing readily available analytical equipment. Using <sup>19</sup>F NMR to determine enantiopurity or to study racemization kinetics has the capability to provide improved sensitivity and resolution for systems that contain other molecular species in the mixture. For example, this <sup>19</sup>F NMR method could be used to study changes in the racemization rate in the presence of various impurities or reagents that may interfere with chromatographic analysis. Additionally, longer elution times are often required to improve the resolution of chromatographic separations for a mixture of enantiomers, whereas high-quality data from the NMR sample can be collected in just a few minutes. The described method provides a valuable addition to the analytical toolkit for studying fluorine-containing chiral compounds.

### ■ ASSOCIATED CONTENT

#### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c03316>.

Details of NMR data acquisition; spectra with CSAs; correlation between HPLC and NMR data; calculations; and comparison of racemization in different physical forms ([PDF](#))

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#### Author Contributions

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#### Notes

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### ■ ABBREVIATIONS

API = active pharmaceutical ingredient; FDA = food and drug administration; NMR = nuclear magnetic resonance; TBPTA = *tert*-butyl(phenyl)phosphinothioic acid; MTPA =  $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic acid; TRISPHAT = tetrabutylammonium tris(3,4,5,6-tetrachlorobenzene-1,2-diato- $\kappa^2$ O<sup>1</sup>,O<sup>2</sup>)phosphorus(V); TiPSY = 3,3'-bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate

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