Chiral Phosphoric Acid Promoted Chiral 1H NMR Analysis of Atropisomeric Quinolines

Junlin Wan, Jun Jiang and Juan Li*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, China

An efficient enantioselective NMR analysis of atropisomeric quinolines in the promotion of chiral phosphoric acid is described, in which a variety of racemic 4-aryl quinolines were well-recognized with up to 0.17 ppm \( \Delta \Delta \delta \) value. Additionally, the optical purities of different nonracemic substrates could be evaluated fast via NMR analysis with high accuracy.

Keywords: chiral recognition, 1H NMR analysis, quinolines, chiral phosphoric acid, chiral shift reagents

INTRODUCTION

Axial chirality is one of the important types of molecular asymmetry created from restriction of carbon–carbon or carbon–nitrogen single-bond rotation. Since Christie and Kenner reported the first detection of atropisomerism in 1922 (Christie and Kenner, 1922), axial chirality was found in a lot of natural products and pharmaceutical compounds as exemplified by michellamines (Manfredi et al., 1991; Bringmann et al., 1993) and vancomycin (Nicolaou et al., 1999). Besides, many chiral ligands and catalysts, such as BINOL, BINAP, and phosphoric acids, have been developed based on axially chiral biaryl scaffolds (Miyashita et al., 1980; Akutagawa, 1995; Kumobayashi et al., 2001; Brunel, 2005; Brunel, 2007; Genet et al., 2014). It is well-known that the enantiopurities of chiral ligands and catalysts are critical to their enantiocontrol, and atropisomers of bioactive molecules always exhibit different pharmacodynamic and pharmacokinetic behavior both in vivo and in vitro (Eichelbaum and Gross, 1996; Clayden et al., 2009). Thus, the development of efficient methods to recognize and determine atropisomeric compounds becomes an interesting target and is always in high demand. As key analysis methods, GC (Schurig and Nowotny, 1990), IR (Reetz et al., 1998), HPLC (Han, 1997), circular dichroism (Ding et al., 1999; Nieto et al., 2008; Ghosn and Wolf, 2009; Nieto et al., 2010), fluorescence spectroscopy (James et al., 1995; Mei and Wolf, 2004; Pu, 2004; Zhao et al., 2004; Tumambac and Wolf, 2005; Liu et al., 2009), electrophoresis technologies (Reetz et al., 2000), and NMR spectroscopy have been efficiently employed in chiral determinations. Among these classic technologies, NMR analysis affords an ideal platform to explore efficient chiral analysis strategies because of its mild condition, easy operation, fast evaluation, high sample tolerance, etc. Over the past few decades, a lot of chiral shift reagents (CSRs) (Frazier et al., 1971; Goering et al., 1971; Yeh et al., 1986; Ghosh et al., 2004; Yang et al., 2005; Mori et al., 2013) or chiral solvating reagents (CSAs) (Pirkle, 1966; Lancelot et al., 1969; Parker, 1991; Wenzel and Wilcox, 2003; Seco et al., 2004; Lovely and Wenzel, 2006; Ema et al., 2007; Wenzel, 2007; Iwaniuk and Wolf, 2010; Moon et al., 2010; Gualandi et al., 2011; Pham and Wenzel, 2011; Quinn et al., 2011; Wenzel and Chisholm, 2011; Ma et al., 2012; Labuta et al., 2013; Zhou et al., 2015; Bian et al., 2016a; Akdeniz et al., 2016; Bian et al., 2016b; Huang et al., 2016) were successfully designed and employed in chiral NMR analysis. Encouraged by these achievements and our continuous efforts to study chiral interactions, we were particularly interested in exploring a novel NMR-based chiral analysis method for our synthetic targets: In 2017, we reported an enantioselective NMR analysis of indoloquinazoline alkaloid–type tertiary alcohols with chiral phosphoric acid (CPA) (Akiyama et al., 2006; Akiyama, 2007; Akiyama...
**FIGURE 1** | Chiral 1H NMR analysis of aryl quinolines with a chiral phosphoric acid.

**TABLE 1** | Evaluating the chiral recognition abilities of chiral phosphoric acids (R)-C with 1a.\(^a\)

| Entry | Chiral shift Reagent | Deuterated Solvents | \(\Delta\Delta\delta\) (ppm) |
|-------|----------------------|---------------------|--------------------------|
| 1     | (R)-C1               | CD\(_2\)OD          | 0.03                     |
| 2     | (R)-C2               | CD\(_2\)OD          | 0.01                     |
| 3     | (R)-C3               | CD\(_2\)OD          | 0                        |
| 4     | (R)-C4               | CD\(_2\)OD          | 0                        |
| 5     | (R)-C5               | CD\(_2\)OD          | 0.01                     |
| 6     | (R)-C6               | CD\(_2\)OD          | 0                        |
| 7     | (R)-C7               | CD\(_2\)OD          | 0                        |
| 8     | (R)-C8               | CD\(_2\)OD          | 0.02                     |
| 9     | (R)-C9               | CD\(_2\)OD          | 0.01                     |
| 10    | (R)-C1               | CDCl\(_3\)          | nd                       |
| 11    | (R)-C1               | DMSO-De             | 0                        |
| 12    | (R)-C1               | DMF-De              | 0                        |
| 13    | (R)-C1               | Acetone-D\(_6\)     | 0.02                     |
| 14    | (R)-C1               | CD_{2}CN            | 0.01                     |
| 15    | (R)-C1               | C\(_6\)D\(_6\)      | 0.1                      |
| 16    | (R)-C1               | CD\(_2\)OD\(_p\)    | 0.03                     |
| 17    | (R)-C1               | CD\(_2\)OD\(_p\)    | 0.02                     |
| 18    | (R)-C1               | CD\(_2\)OD\(_p\)    | 0.05                     |

\(^a\)Unless otherwise noted, all samples were prepared by mixing (R)-C (0.01 mmol) and the guests 2a (0.01 mmol) in CD\(_2\)OD (0.5 mL) at 25°C.  
\(^b\)0.1 mL CDCl\(_3\) was added.  
\(^c\)0.5 equiv. of (R)-C1 was used.  
\(^d\)2 equiv. of (R)-C1 was used.
**TABLE 2** | Measurements of 1H chemical shift nonequivalences (ΔΔδ) of racemic aryl quinolinones.a

| Entry | Aryl quinolinone | Spectra | ΔΔδ (ppm) |
|-------|------------------|---------|-----------|
| 1b    | ![Aryl quinolinone 1b](image1) | ![Spectra 1b](image2) | 0.11 |
| 2     | ![Aryl quinolinone 2](image3) | ![Spectra 2](image4) | 0.06 |
| 3b    | ![Aryl quinolinone 3b](image5) | ![Spectra 3b](image6) | 0.17 |
| 4     | ![Aryl quinolinone 4](image7) | ![Spectra 4](image8) | 0.02 |
| 5b    | ![Aryl quinolinone 5b](image9) | ![Spectra 5b](image10) | 0.06 |
| 6b    | ![Aryl quinolinone 6b](image11) | ![Spectra 6b](image12) | 0.17 |
| 7     | ![Aryl quinolinone 7](image13) | ![Spectra 7](image14) | 0.06 |
| 8b    | ![Aryl quinolinone 8b](image15) | ![Spectra 8b](image16) | 0.02 |
| 9     | ![Aryl quinolinone 9](image17) | ![Spectra 9](image18) | 0.07 |

(Continued on following page)
TABLE 2 | Measurements of 1H chemical shift nonequivalences (ΔΔδ) of racemic aryl quinolinones.\textsuperscript{a}

| Entry | Aryl quinolinone | Spectra | ΔΔδ (ppm) |
|-------|------------------|---------|-----------|
| 10    | ![Structure 10](image) | ![Spectrum 10](image) | 0.04 |
| 11\textsuperscript{b} | ![Structure 11](image) | ![Spectrum 11](image) | 0.04 |
| 12    | ![Structure 12](image) | ![Spectrum 12](image) | 0.04 |
| 13    | ![Structure 13](image) | ![Spectrum 13](image) | 0.01 |
| 14    | ![Structure 14](image) | ![Spectrum 14](image) | 0.03 |
| 15    | ![Structure 15](image) | ![Spectrum 15](image) | 0.05 |
| 16    | ![Structure 16](image) | ![Spectrum 16](image) | 0.06 |
| 17    | ![Structure 17](image) | ![Spectrum 17](image) | 0.06 |

(Continued on following page)
TABLE 2 | (Continued) Measurements of 1H chemical shift nonequivalences (DDδ) of racemic aryl quinolinones.*

| Entry | Aryl quinolinone | Spectra | ΔΔδ (ppm) |
|-------|------------------|---------|-----------|
| 18b   | ![Image](https://example.com/figure1.png) | ![Image](https://example.com/figure2.png) | 0.07       |

*Unless otherwise noted, all samples were prepared by mixing (R)-C1 (0.01 mmol) and the guests 2 (0.01 mmol) in CD$_3$OD (0.5 ml) and CDCl$_3$ (0.1 ml) at 25°C.

RESULTS AND DISCUSSION

As shown in Figure 1, the methyl peak on the benzyl position of racemic 1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl) ethan-1-one 1a is unimodal on 1H NMR spectrum in the...
absence of chiral phosphoric acid. Generally, the addition of 1 equivalent of chiral phosphoric acid brought obvious chemical shift nonequivalences of this methyl peak of 1a, suggesting the strong chiral interaction between chiral phosphoric acids and 4-aryl quinoline. It was shown that the substituents on phosphoric acids had obvious influence on the recognition. For example, 3,3′-α-naphthyl-substituted phosphoric acid C1 afforded a baseline resolution and the largest chemical shift nonequivalence (\(\Delta\Delta\delta = 0.03\)) of a methyl H signal of 1a in CD3OD at 25°C, while 3,3′-phenyl-substituted phosphoric acid C7 failed to differentiate atropisomers of 1a. Besides, deuterated solvents also played an important role in chiral recognition. As shown in Table 1, chemical shift nonequivalence of methyl H of 1a’s atropisomers was observed when CPA C1 and 1a were combined in CD2Cl2, acetone-D6, CD3CN, and CD3OD, while highly polar solvent, such as DMF-D7 and DMSO-D6, seemed to break the interaction between the chiral sensor and analyte, resulting in no differentiation of atropisomers. Besides, different peaks overlapped together when CDCl3 was employed as solvent. Significantly, CD6D6 enabled the best chiral recognition of up to 0.1 ppm, albeit with poor solubility of CPA and quinoline analytes. Considering the fact that CPA and quinoline mixture dissolve well in CDCl3, binary solvents of CD3OD and CDCl3 (5/1) were chosen as analysis media in the purpose of balancing solubility and recognition, offering eminent solubility and baseline resolution (entry 16). Additionally, the amount of 1a also influenced differentiation; for example, baseline resolution was not achieved when a 0.5 equivalent of chiral phosphoric acid C1 was used, while increasing the amount of C1 to 2 equivalent resulted in larger chemical shift nonequivalence (\(\Delta\Delta\delta = 0.05\)). Finally, under the balance of atom economy and recognition, 1 equivalent of (R)-C1 was employed as a chiral sensor (entry 17).

Under optimized conditions, a series of 4-aryl quinoline guests were tested. First, the influence of substituents on quinoline (ring 1) was evaluated. It was shown that different electron-withdrawing groups on ring 1 were fit well under standard conditions, providing baseline resolutions and 0.02–0.17 ppm \(\Delta\Delta\delta\) values, respectively (Table 2, entries 1–5). Besides, different R3 groups on quinoline such as acetyl, ethyl formate, methyl formate and trifluoroacetyl were also tested, all of which led to clear recognition of atropisomers with up to 0.07 ppm \(\Delta\Delta\delta\) values. Subsequently, different 4-aryl groups (ring 2) were also studied. As shown in Table 2, a variety of electron-withdrawing or electron-donating groups on ring 2 were well-tolerated, and substituents with either moderate or bulky size on the 2′-position of ring 2 all resulted in clear baseline resolution with good chemical shift nonequivalences. Noticeably, when 1-[(1,1′-biphenyl)-2-yl]-2-methylquinolin-3-yl] ethan-1-one 1g was employed as analyte, the largest chemical shift nonequivalence of 0.17 ppm \(\Delta\Delta\delta\) was obtained. Interestingly, when 1k–1n were employed as guests, obvious split peaks on \(\alpha\)-H of oxygen were observed. It is also worth noting that nitro-substituted substrates 1b and 1g also afforded good differentiation results (chemical shift nonequivalence of 0.11 and 0.17 ppm \(\Delta\Delta\delta\), respectively), possibly due to the steric hindrance effect of nitro group.

With this optimal recognition condition, the possibility of our methodology in the enantiomeric determination of various nonracemic quinolines was successfully developed. With this method, atropisomers of various quinolines were well-discriminated with base resolution; besides, the optical purities of different nonracemic quinoline 1j could be evaluated fast with high accuracy. This method broadens the chiral analysis ability of chiral phosphoric acids, which encourages us to further explore the interaction of chiral acids with different analytes.

**CONCLUSION**

In conclusion, an efficient phosphoric acid–promoted chiral recognition of atropisomeric quinolines via NMR analysis was successfully developed. With this method, atropisomers of various quinolines were well-discriminated with base resolution; besides, the optical purities of different nonracemic quinoline 1j could be evaluated fast with high accuracy. This method broadens the chiral analysis ability of chiral phosphoric acids, which encourages us to further explore the interaction of chiral acids with different analytes.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

**FUNDING**

This research was financially supported by Major Research Plan of Wenzhou City (No. ZG2017027).

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2021.672704/full#supplementary-material
