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^{31}P NMR Based Method for Determining Enantiopurity of Chiral Phosphoric Acids and Its Application to the BINOL- and H8-BINOL-Based Chiral Phosphoric Acid Thermal Racemization Studies

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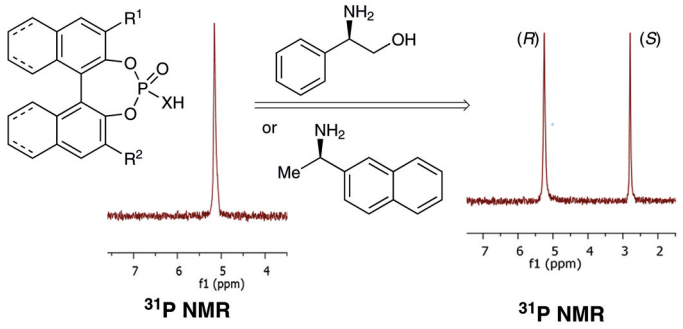
We dedicate this Letter to Professor James D. White on the occasion of his 80th birthday



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Abstract A simple and reliable protocol for determining the enantiopurity of 3,3′-substituted BINOL- and H8-BINOL-based chiral phosphoric acids (CPA) using ^{31}P NMR spectroscopy in the presence of chiral amines as the discriminating agents is described. The generality of this method is demonstrated using nine common BINOL- and H8-BINOL-based chiral acids. This technique was utilized for monitoring the extent of racemization of 3,5-$(F_3C)_2C_6H_3$-substituted BINOL- and H8-BINOL-based CPA at 200, 220, and 250 °C.

Key words chiral phosphoric acid, racemization, enantiopurity, ^{31}P NMR

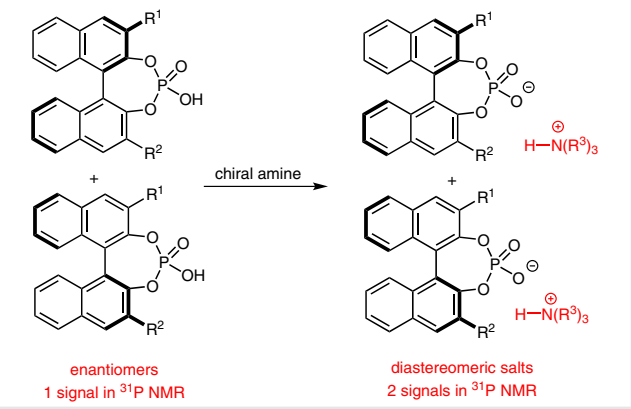
In recent years chiral organic Brønsted acids have emerged as powerful, broadly applicable, and practical catalysts for a variety of asymmetric transformations.[1] In particular, a considerable attention has been devoted to the studies of chiral phosphoric acids (CPA).[2] Although a number of new and interesting chiral scaffolds for CPA have emerged as a result of these studies,[3] the BINOL- and H8-BINOL-derived CPA have been highly utilized due to their tunability, conformational rigidity, C_2-symmetry, and availability of the catalysts and building blocks.

Our group has a long-standing interest in exploring new organic transformations catalyzed by Brønsted acids,[4] and our experience in Brønsted acid catalysis suggests that these endeavors can significantly benefit from the improvements in the preparation and characterization of the catalysts. Thus, some of our recent efforts have been directed to simplifying the generation of CPA. Recently, we reported a direct redox-based method allowing a single-step interconversion of the BINOL-based CPA into their H8-BINOL-based counterparts.[5] These redox interconversions were conducted at elevated temperatures or in the presence of transition metal catalysts such as platinum(IV) oxide, which, in some instances, is known to cause the racemization of BINOL or H8-BINOL.[6] In the attempts to determine the enantiomeric excess of the CPA generated in these studies, we realized that there is no simple method for CPA enantiopurity assessment, and there is little information on the sensitivity of BINOL- or H8-BINOL-based CPA to racemization available.

In general, HPLC analysis is one of the most reliable techniques for determining the enantiopurity of chiral compounds, and the use of reverse-phase HPLC for the analysis of CPA enantiopurity is precedented.[7] However, HPLC analysis may require the use of specialized equipment (i.e., chromatography columns) that is not always readily available, the analysis is CPA specific, and the development of HPLC assays may be time consuming due to the large number of parameters to optimize (i.e., column type, eluent composition, flow rate, etc.). Alternatively, optical rotation measurement can be used to determine the enantiopurity of CPA with previously reported specific optical rotation values; however, very limited information on the specific optical rotation of CPA is available in the literature. At the same time, optical-rotation-based analysis is not always reliable due to the high sensitivity of such measurements to the presence of phosphate salts impurities.[7,8] The realization of these limitations has inspired us to develop an alternative ^{31}P NMR based method to assess the enantiopurity of CPA in the presence of chiral amines as the discriminating agents. This manuscript describes the use of this method for the fast, operationally simple, and reliable measurement of enantiomeric excess for nine BINOL- and H8-BINOL-derived chiral acids as well as the application of this technique to investigate the thermal racemization of 3,5-$(F_3C)_2C_6H_3$-substituted BINOL- and H8-BINOL-based CPA.

Chiral phosphoric acids have been of great utility for the resolution of chiral amines, and the diastereomeric ammonium phosphates often possess distinctly different physical

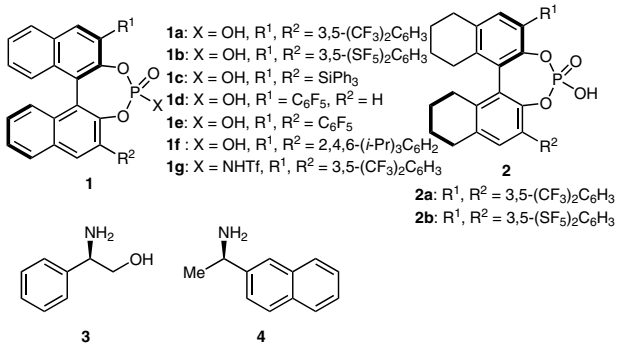
properties such as spectral characteristics, melting points, etc.[9] Due to the aforementioned reasons, CPA were identified as the valuable chiral complexing agents, and the use of 1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPPA) for determining the enantiopurity of various alkaloids and amines by ^{1}H NMR is well precedented.[10] Similarly, various chiral phosphorus(V) or phosphorus(III) reagents have a long-standing history as useful NMR-discriminating agents for ^{1}H NMR and ^{31}P NMR based analysis of enantioenriched alcohols, diols, amines, amino alcohols, and hydroxy acids.[11] However, to our knowledge, the reverse analysis (i.e., determination of enantiopurity of CPA by ^{31}P NMR spectroscopy in the presence of chiral discriminating agent) has not been described. Based on the aforementioned precedents, we surmised that when combined with a mixture of CPA, chiral amines would undergo irreversible protonation to form diastereomeric ammonium phosphates, which will produce a pair of ^{31}P NMR signals (Scheme 1). Considering the simplicity of the CPA ^{31}P NMR spectra, the enantiopurity of CPA can be conveniently measured by the integration of the corresponding ^{31}P NMR signals. While the idea is simple, such application of NMR discrimination, to our knowledge, has not been previously reported.



Scheme 1 Proposed ^{31}P NMR based analysis of enantiomeric phosphoric acids in the presence of an amine as the chiral discriminating agent

After preliminary testing, commercially available amino alcohol **3** was identified as a suitable chiral discriminating agent (Table 1). Upon combining the mixtures of various (*R*)- and (*S*)-CPA with 1.5 equivalents of **3** in deuterated solvent, we indeed observed two nonequivalent signals in the ^{31}P NMR spectra. Importantly, good resolution of the diastereomeric phosphate signals was observed for the majority of the tested CPA (Table 1, entries 1–4) with the exception of acids **1e** and **1f**. In the cases of acids **1e** and **1f**, the resolution was found to be insufficient for the accurate integration of the signals. However, this problem can be circumvented if commercially available amine **4** is employed as the chiral discriminating agent (Table 1, entries 5 and 6). In addition, commonly used commercially available acids **1a** and **1f** were tested at lower concentrations (Table 1, entries 1 and 6). Similarly, well-resolved diastereomeric ^{31}P NMR phosphate signals were observed at the lower concentrations although a minor concentration-dependent drift in Δδ was noticed for **1f**. The method can be applied not only to CPA, but also to *N*-triflyl amides (Table 1, entry 7) although somewhat lower resolution of diastereomeric phosphoramides (ca. 40 Hz) was observed when acid **1g** was combined with amine **3**. Finally, the diastereomeric phosphate salts obtained by combining amine **3** with H8-BINOL backbone-containing CPA **2a** and **2b** exhibited well-resolved diastereomeric phosphate peaks in the ^{31}P NMR spectra (Table 1, entries 8 and 9). The results from Table 1 suggest that amines **3** and **4** serve as excellent chiral discriminating agents and provide good resolution of the enantiomeric phosphate peaks in ^{31}P NMR spectra upon mixing with CPA. To demonstrate that the enantiomeric excesses determined

Table 1 Differences in ^{31}P Chemical Shift (Δδ) between Enantiomers of Chiral Phosphorous Acids in the Presence of Chiral Amines as Discriminating agents



Entry	CPA[a]	Discriminating agent	Δδ (ppm)	Δδ (Hz)[b]
1	**1a**[c]	**3** **3**	2.69 (23 mM) 2.67 (4.3 mM)	761 (23 mM) 754 (4.3 mM)
2	**1b**	**3**	2.57	727
3	**1c**	**3**	0.74	209
4	**1d**	**3**	0.20	57
5	**1e**	**4**	0.85	241
6	**1f**[d]	**4** **4**	0.59 (13 mM) 1.51 (4.7 mM)	167 (13 mM) 244 (4.7 mM)
7	**1g**	**3**	0.14	40
8	**2a**	**3**	2.43	688
9	**2b**	**3**	2.23	631

[a] NMR samples consist of 10 mg (0.015–0.010 mmol) of nonracemic mixture of CPA's enantiomers and 1.5 equiv of discriminating agent dissolved in 0.6 mL of $CDCl_3$ (25–17 mM).
[b] ^{31}P NMR (283 MHz) spectra were measured on a Varian VNRMS 700 MHz at r.t.
[c] Samples were tested at 23 mM and 4.3 mM concentrations.
[d] Sample were tested at 13 mM (283 MHz) and 2.8 mM concentrations (162 MHz).

by the integration of the ^{31}P NMR peaks of diastereomeric phosphates correspond to the actual enantiopurity of the sample, we constructed a graph with the actual enantiopurity of **1a** (i.e., the ee) plotted against the ee established by NMR spectroscopy (Figure 1). Gratifyingly, an excellent linear correlation ($R^2 = 0.999$) was obtained for these measurements, and the average absolute error of the measurements was found to be less than 1.1% (cf. Supporting Information).

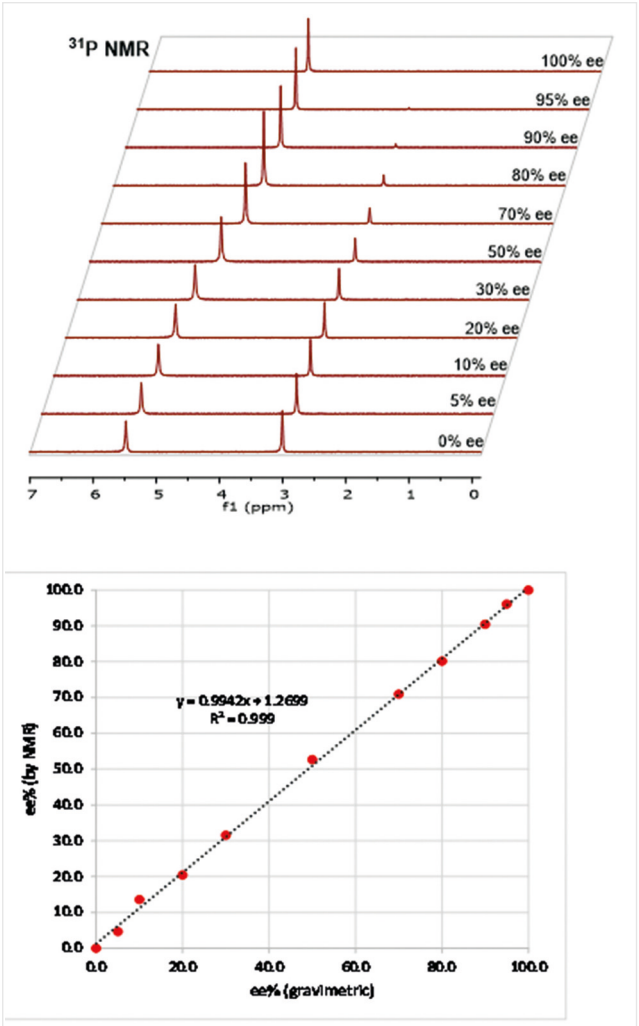
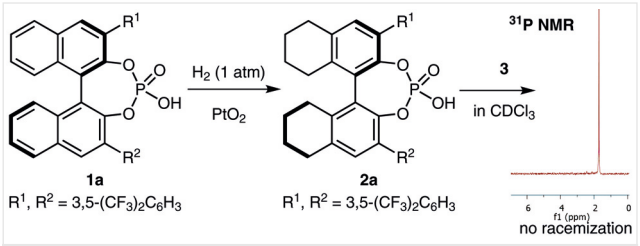


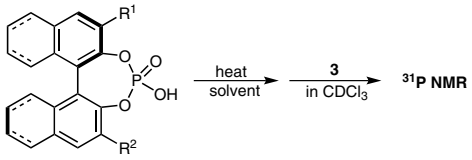
Figure 1 ^{31}P NMR spectra of nonracemic **1a** and discriminating agent **3** in $CDCl_3$. The plot demonstrates the linear correlation between %ee determined gravimetrically and through the integration of nonequivalent ^{31}P NMR signals.

With a direct NMR method for the measurement of enantiopurity of CPA in hand, the stability of CPA to racemization was investigated next (Scheme 2 and Table 2). Recently, our group reported a new method for the direct hydrogenation of BINOL-based CPA to their H8-BINOL counterparts using PtO_2 as the catalyst.[5] In order to verify the stability of CPA to racemization under the reduction conditions, we had to reductively remove the phosphate functionality with $LiAlH_4$, and then analyzed the resultant H8-BINOL using HPLC techniques. However, assessing the enantiopurity of **2a** by ^{31}P NMR spectroscopy in the presence of chiral amine **3** provided a significantly faster and more convenient approach (Scheme 2). Consistent with our prior findings, no epimerization of **1a** or **2a** was detected under the hydrogenation conditions.



Scheme 2 Application of chiral discriminating agent in evaluation of CPA enantiomeric excess after hydrogenation reaction

Table 2 Application of Discriminating Agent in the Study of CPA Epimerization under Thermal Conditions



Entry	CPA	Solvent	Temp (°C)[a]	Time (h)	ee (%) by NMR[b]
1	**1a**	1,2-dichlorobenzene	200	24	96
2	**1a**	1,2-dichlorobenzene	220	18	84
3	**1a**	biphenyl	250	24	–[c]
4	**2a**	1,2-dichlorobenzene	220	18	>99

[a] Mixtures were heated in sealed 1 dram vials.
[b] Average of two runs is reported.
[c] Not determined. Substrate decomposed.

The thermal racemization of CPA was investigated next. It is known that 1,1′-binaphthalene-2,2′-diol epimerizes when being heated ($t_{1/2}$ = 60 min at 220 °C).[12] A study on racemization of BINOL-derived methyl phosphate ester suggests that it also undergoes racemization under elevated temperatures, and the racemization rate is similar to the one of BINOL ($t_{1/2}$ = 100 min at 220 °C).[13] While it is commonly assumed that CPA are more thermally stable then BINOL derivatives, to our knowledge no studies on thermal racemization of BINOL- or H8-BINOL-derived phosphoric acids is available. Thus, we conducted experiments to determine the extend of racemization of BINOL-derived acid **1a** and its H8-BINOL-derived counterpart **2a** at elevated temperatures (Table 2). When subjected to heating in 1,2-dichlorobenzene at 200 °C, acid **1a** did undergo racemization; however, the rate of this atropisomerization was sig-

nificantly lower than for BINOL- or BINOL-derived methyl phosphate (Table 2, entry 1). Thus, only 4% loss in enantiomeric excess was observed after 24 hours. The increase in temperature to 220 °C resulted in a faster racemization rate, and the measured enantiopurity of **1a** was 84% ee after 18 hours (Table 2, entry 2). Further elevation of the temperature to 250 °C resulted in decomposition of **1a** (Table 1, entry 3). Interestingly, the H8-BINOL counterpart of **1a**, acid **2a** exhibited higher stability to racemization, and the enantiopure sample for **2a** was isolated even after being heated at 220 °C for 18 hours (Table 2, entry 4). These experiments demonstrate that BINOL-based CPA with saturated backbone is more configurationally stable in comparison to its unsaturated analogue, which is consistent with the prior studies on comparative racemization of H8-BINOL and BINOL derivatives.[14]

In conclusion, we have developed a quick, easy, and reliable protocol[15] to determine the enantiopurity of chiral phosphoric acids using ^{31}P NMR spectroscopy and commercially available chiral amines as discriminating agents. The protocol is shown to be general for a series of CPA and it gives excellent resolution in most cases. Utilizing this protocol, we were able to study the racemization behavior of chiral phosphoric acids under hydrogenation and thermal conditions.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560547.

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(15) **General Procedures for the NMR Discrimination Experiments**
Nonracemic CPA (10 mg) was mixed with discriminating agent (1.5 equiv) in $CDCl_3$ (0.6 mL) in NMR tubes (all CPA was washed with 6 N HCl prior to analysis). The ^{31}P spectrum of the mixture was measured using a Varian VNRMS 700.