Synthesis of TRIP and Analysis of Phosphate Salt Impurities

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Abstract: The chiral phosphoric acid TRIP, a useful Brønsted acid catalyst, easily becomes contaminated with metal impurities in the form of phosphate salts during synthesis. This significantly reduces the content of free acid in the product which can hamper the catalytic activity. Methods to easily judge whether TRIP contains mainly the free acid or phosphate salts are presented, using ^{1}H NMR spectroscopy or a simple pH test. An improved synthetic protocol for TRIP was established that reliably produces the free acid.

Key words: asymmetric catalysis, phosphates, imine hydrogenation, Brønsted acids, organocatalysis

In recent years, relatively strong chiral Brønsted acids have emerged as powerful catalysts for many asymmetric transformations.[1] Particularly effective are phosphoric acids **1** with an axially chiral binaphthyl backbone bearing sterically demanding substituents in the 3-positions, first introduced as catalysts by Akiyama and Terada[2] (Figure 1). Among the many differently substituted binaphthyl-phosphoric acids, 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**2**, abbreviated TRIP), emerged as a particularly powerful one in terms of activity and stereoselectivity.[3]

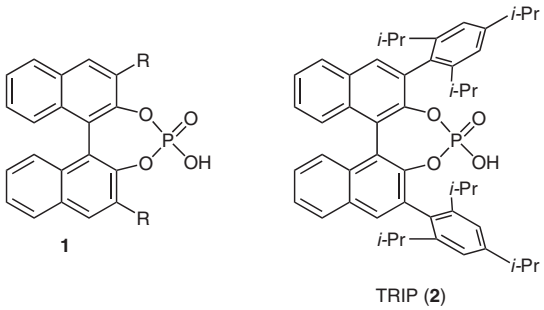

Figure 1 Chiral binaphthyl phosphoric acids: general structure **1** and TRIP **2**

TRIP was first introduced for the asymmetric transfer hydrogenation of imines.[4] Other notable applications in which TRIP turned out to be the best asymmetric Brønsted acid catalyst include the reductive amination of α-branched aldehydes,[5] an aldol conjugate reduction–reductive amination cascade,[6] Friedel–Crafts and Pictet–Spengler reactions[7] and cycloadditions.[8]

In the aforementioned reactions, asymmetry was introduced by the conjugate base of TRIP **2**. The chiral phosphate can also effect stereoselectivity if employed in the form of salts in reactions with cationic intermediates,[9] a strategy also termed asymmetric counteranion directed catalysis (ACDC).[10] The TRIP anion has proven to induce high levels of stereoselectivity in combination with organic counterions, for example, in the transfer hydrogenation and epoxidation of α,β-unsatured aldehydes[10,11] and ketones,[12] respectively. The use of the TRIP anion in otherwise achiral transition-metal complexes enabled asymmetric gold-catalyzed allene cyclizations[13] and palladium-catalyzed allylic alkylations[14] with high levels of stereoselectivity. Furthermore, TRIP was also the catalyst of choice in combinations of Brønsted acid and transition-metal catalysis.[15]

Interestingly, alkali or alkaline earth salts of chiral phosphates **1** can also be efficient catalysts.[16] Feng and coworkers reported the use of sodium salts of **1** in an enantioselective Strecker reaction[16b] and Ishihara and coworkers reported the use of alkali or alkaline earth salts for an enantioselective cyanosilylation of ketones[16a] and a Mannich reaction.[16c] In all these cases, the chiral induction was dependent on the metal counterion and the mode of preparation of the salts.

Lately, Ishihara pointed out the possible salt formation and contamination of BINOL-derived phosphoric acids **1** during purification on silica gel and warned that such impurities might have a substantial influence on the catalyst's performance.[16c] Other groups working with chiral Brønsted acids had observed similar phenomena. Ding and coworkers found that washing the catalyst with HCl improved the activity, obviously by regenerating some free acid from its salt.[17] Rueping and coworkers discussed the possibility that a calcium salt of the chiral phosphate was the actual catalyst.[18] Here we present findings from our own laboratory regarding this matter and an improved synthetic protocol for TRIP.

The synthesis of TRIP followed established synthetic procedures[2,19] and the compound has become commercially available in the meantime. However, during our initial studies we sometimes noticed small differences between batches of TRIP synthesized in our laboratories. These seemed to relate to a partial salt formation of TRIP. In order to establish a reliable synthetic method for TRIP and other chiral phosophoric acids and to provide a uniform quality of the compound for research, we investigated this situation in detail.

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Initially, we had noticed differences in the ^{1}H NMR spectra of TRIP synthesized in our laboratories. Although each NMR spectrum was satisfying in itself as were the results from mass spectroscopy, the ^{1}H NMR spectra were not always identical. We found two types of batches, **A** and **B**, that were best distinguishable by the pattern of the isopropyl CH signals (Figure 2).

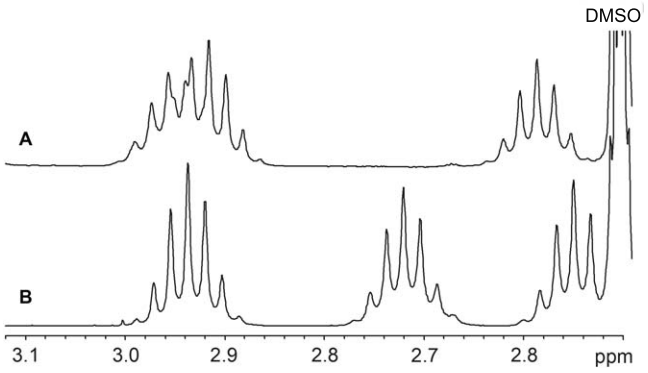


Figure 2 Excerpt of the ^{1}H NMR spectra of two different batches of TRIP in DMSO-d_6, type **A** and **B**

TRIP of batch **A** showed two signals of four and two protons while batch **B** showed three separate signals of two protons each for the six isopropyl CH groups. DMSO-d_6 was the most suitable solvent to see this difference, but other solvents could be used as well (see Supporting Information). This finding prompted us to investigate the reason behind these differences, although in asymmetric reactions, the two kinds of TRIP seemed to behave similarly.

The addition of small amounts of water or different solvents did not change the spectra of either type of TRIP, so such impurities could be ruled out as the reason for the difference. However, we found that addition of acid or base had a significant effect. Adding either ammonia or pyridine to TRIP of type **B** shifted the peaks in the NMR to look like type **A**. Adding HCl to TRIP of type **A** resulted in a ^{1}H NMR of type **B**. Adding acid to type **B** or base to type **A** did not induce a shift in the signals. Clearly, type **B** is the free acid while type **A** is at least partially a phosphate salt.

A quick test with pH paper supported this assumption, as a solution of type **B** TRIP in methanol gave a pH of ca. 1–2, while type **A** TRIP was only mildly acidic with a pH of around 5 (Figure 3).

The nature of the base added in the above NMR experiments had no further effect on the signals of TRIP. As no organic impurity could be detected in the NMR spectra of type **A** batches, we presumed them to be inorganic salts. A trace element analysis by ICP-OES revealed various alkali and alkaline earth metals to be present as major impurity but also several other metals. Most notably, silicon was found, a likely impurity from silica gel chromatography. Type **B** revealed only traces of metal impurities apart from silicon, again supporting that it is the free acid (Table 1).

Figure 3 Testing the different batches of TRIP with pH paper. Left: type **B**, right: type **A**.

Table 1 Trace Element Analysis by ICP-OES[a]

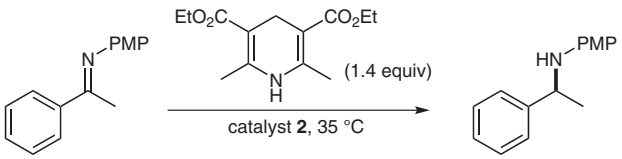
Batch	Na	K	Mg	Ca	Al	Si	Fe	Pd	Zn
A	6151	29	3590	7482	<5	560	15	7	5
B	16	13	20	83	20	725	9	<5	<5

[a] Values in ppm.

Most likely, not all of these metal impurities were present as TRIP salts. Especially Si probably occurred in some form of silica, leftover from chromatographic purification. Nevertheless, if one assumes the other metals to be present exclusively as salts with one to three TRIP anions depending on the oxidation state of the metal, an estimated amount of 81% of type **A** TRIP would be present in the form of a salt. For type **B**, one arrives at only around 1% of salt. These values are an estimation of the maximum amount of salt only, but they support the assumption that type **A** is mainly a salt with some free acid present while type **B** is the desired free acid **2**.

The question arose as to whether the unintended use of salt-containing TRIP in catalytic reactions had influenced the reaction outcome. We compared the performance of both types of TRIP as catalysts in an asymmetric transfer hydrogenation (Table 2).[4a]

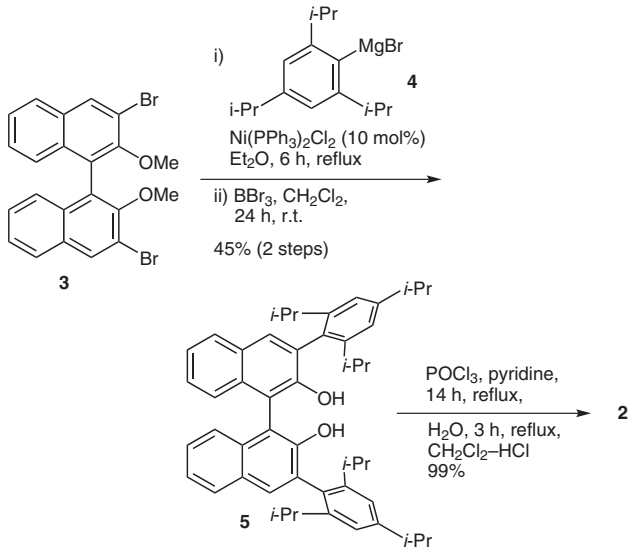
Table 2 Asymmetric Transfer Hydrogenation of Imines



Entry	TRIP (mol%)	Solvent	Time (h)	Conv. (%)	ee (%)
1	**A** (1.0)	toluene	2.5	31	88
2	**A** (1.0)	toluene	24	>95	88
3	**B** (1.0)	toluene	3	96	88

Both the partial salt and the free acid of TRIP catalyzed the reaction to give the chiral amine with the same enantiomeric excess of 88% (Table 2, entries 1–3). But the free acid was significantly more active: within 3 hours, essentially full conversion was reached (Table 2, entry 3) while with using the partial salt **A**, only 31% conversion was reached within the same time and it took 24 hours for full conversion (Table 2, entries 1 and 2).

The main source of the metal impurities found in TRIP **A** could not unambigously be determined. We presume that either chromatographic purification on silica gel or the various metal-containing reagents during the synthesis are responsible. Nevertheless, we developed an improved synthetic method for TRIP that would reliably yield the free acid (Scheme 1, also see the Supporting Information).



Scheme 1

Starting from compound **3**, the triisopropylphenyl groups were introduced by a nickel-catalyzed Kumada coupling with preformed Grignard reagent **4**. Deprotection of the phenolic hydroxyl groups with BBr_3 gave the diol **5** in 45% yield over two steps. Introduction of the phosphoric acid group was achieved by reaction with phosphoryl chloride followed by hydrolysis, giving **2** in nearly quantitative yield. Key to receiving the free acid in pure form was a thorough washing of TRIP with hydrochloric acid after the final step. The product received in this way could easily be crystallized from acetonitrile in contrast to batches containing a mixed salt. Thus, we could obtain single crystals suitable for X-ray crystallography (see the Supporting Information).[20]

These findings should be useful for the synthesis of other strong organic Brønsted acids, too. A quick analysis with pH paper will give a first estimate whether the product is mainly the desired acid or has transformed into a salt. A more precise but still fast analysis can be performed by NMR: treating a sample of the Brønsted acid with excess of HCl and a base will give the free acid and the salt, respectively, which can now be used as references. These tests can be performed directly in the NMR tube as well.

In summary, we have been able to show that the chiral phosphoric acid TRIP easily becomes contaminated with metal impurities during the synthesis, leading to a product containing phosphate salts. This significantly reduces the content of free acid in the product which can appreciably hamper the catalytic activity. We found methods to easily judge the quality of TRIP with respect to the salt content, using ^{1}H NMR spectroscopy or simply pH paper. An improved synthetic protocol for TRIP was established that reliably produces the free acid.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(20) CCDC 777645 contains the supplementary crystallographic data for TRIP·MeCN·0.5H_2O. These data can be obtained from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.