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Highly Acidic BINOL-Derived Phosphoramidimidates and their Application in the Brønsted Acid Catalyzed Synthesis of α-Tocopherol

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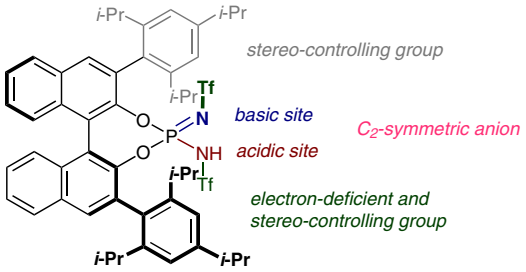
Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday



phosphoramidimidate

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Abstract The design and synthesis of highly acidic BINOL-derived *N*,*N*′-bistriflylphosphoramidimidate and *N*,*N*′-bisarylsulfonylphosphoramidimidate Brønsted acid catalysts are reported.

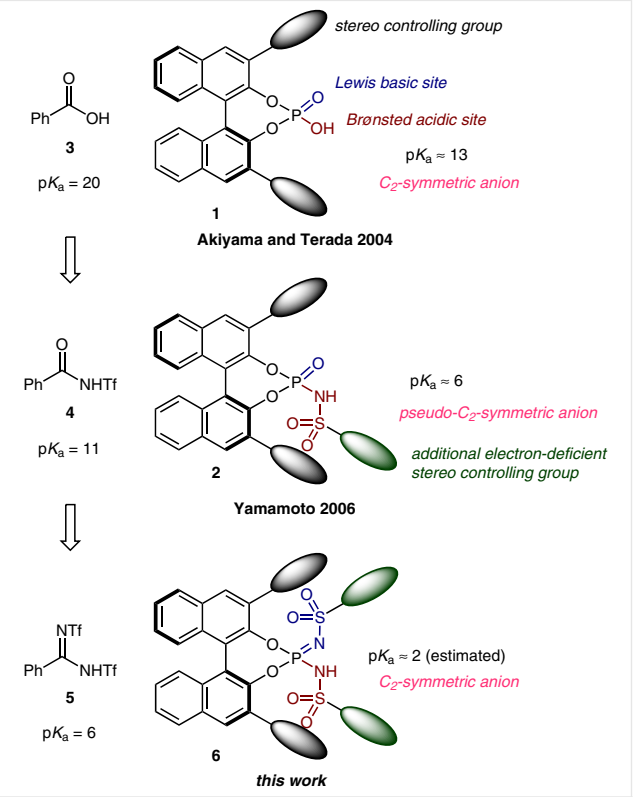
Key words *N*,*N*′-bistriflylphosphoramidimidate, *N*,*N*′-bisarylsulfonylphosphoramidimidate, BINOL-derived, chiral Brønsted acid, C_2-symmetric anions

Within the last ten years, BINOL-derived phosphoric acids **1** have become highly privileged motifs in asymmetric Brønsted acid catalysis.[1–5] In 2004, Akiyama[6] and Terada[7] introduced this catalyst class, setting the road for the current dominance of phosphoric acids in modern organocatalysis.[8] Chiral Brønsted acids have since been demonstrated to be highly efficient and versatile catalysts for a continuously expanding list of challenges in asymmetric synthesis.[1–3,5] One key reason for this success has been the facile structure modulation of phosphoric acids **1** enabling the fine tuning of electronic and steric properties.[6] The acidic functional group is located in a well-defined space, inducing stereochemical information provided by the chiral backbone onto the substrate placed in the catalytically active pocket.[1,3] Furthermore, the utility in diverse reactions is achieved by manifold activation modes, including bifunctional activation, in addition to pure Brønsted acidity.[1–3,5,9] Yet Brønsted acids **1** activate only a limited number of relatively basic functional groups, typically imines.[1–3,5] The development of more acidic chiral acids is crucial towards expanding the applicability of asymmetric Brønsted acid catalysis towards less basic substrates, such as ketones, aldehydes, or olefins. In this context, phosphoramides **2** have recently been introduced by Yamamoto et al. for cases in which phosphoric acids are not acidic enough to activate a specific substrate.[10] Herein we disclose the design and synthesis of BINOL-derived *N*,*N*′-bistriflylphosphoramidimidates and *N*,*N*′-bisarylsulfonylphosphoramidimidates as a new class of highly acidic Brønsted acid catalysts.

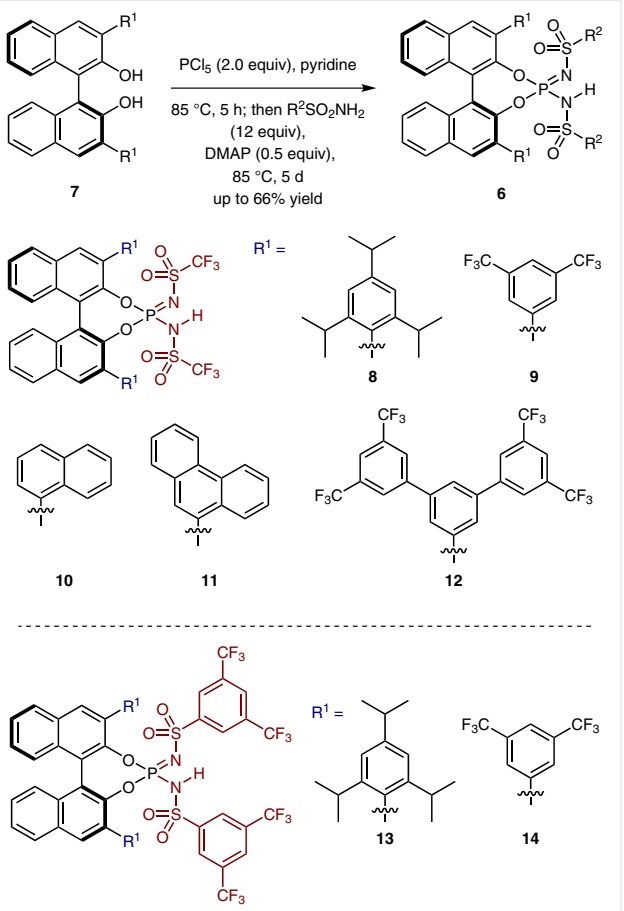
Key to the design of Brønsted acid catalysts that are more acidic than the established phosphoric acids is to increase the stability of the corresponding counteranion.[10] Unfortunately, systematic studies on the acidities and pK_a values of phosphoric acids and their derivatives are relatively scarce. Furthermore, these investigations were typically conducted in solvents such as acetonitrile (MeCN) and dimethyl sulfoxide (DMSO) that are generally unfavorable for asymmetric Brønsted acid catalysis.[11] Detailed studies on the stability and acidity of Brønsted acids, in particular benzoic acid derivatives, were reported by Yagupolskii (Scheme 1).[12] Here the replacement of an oxo group[13] with a stronger electron acceptor, such as the NSO_2CF_3 group (NTf), significantly increased the stability of the counteranions and the acidity of the corresponding acids.[10,12] The acidity increases from benzoic acid (**3**, pK_a = 20 in MeCN)[14] to *N*-triflyl benzamide (**4**, pK_a = 11 in MeCN), and even further to *N*,*N*′-bis-triflyl benzimidamide (**5**, pK_a = 6 in MeCN), illustrating the high potential of this approach.[12]

This general strategy has also been exploited in phosphoramides **2**.[10] However, in their deprotonated form, acids **2** lack the superior C_2-symmetry of BINOL phosphates, potentially limiting their general applicability.[15] We therefore felt that even more acidic and symmetric chiral Brønsted acids such as bissulfonylphosphoramidimidates **6** that, as compared to acids **2**,[13] also feature one additional electron-deficient and potentially stereocontrolling group, were highly desirable subjects for study.[1–3,5]

A careful literature research revealed only a single bissulfonylphosphoramidimidate. In 1980, Kukhar et al. described the synthesis of an achiral pyrocatechol derived



Scheme 1 Influence on pK_a values by introduction of electron-accepting groups (pK_a in MeCN) and highly acidic BINOL-derived phosphoramidimidate Brønsted acids **6**; Tf = SO_2CF_3

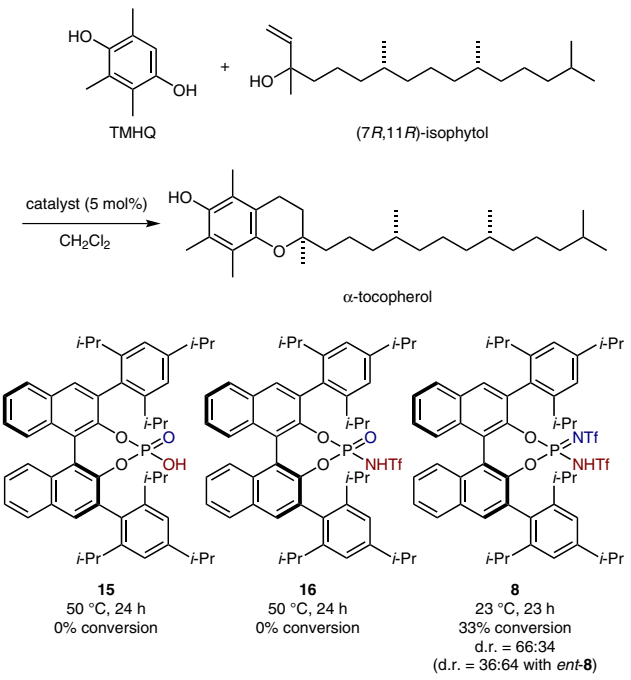


Scheme 2 General synthesis of new phosphoramidimidate Brønsted acids **6**

N,*N*′-bistriflylphosphoramidimidate in two steps.[16] A retrosynthetic analysis of our desired phosphoramidimidate **6** furnished differently substituted moisture-sensitive phosphorus precursors and the corresponding BINOLs **7**. A direct substitution approach on phosphorus(V) led us to start from commercially available PCl_5. We speculated that treatment of the corresponding BINOL derivative **7** in hot pyridine with PCl_5 should generate the corresponding pentavalent compound [$(RO)_2PCl_3$]. This intermediate should then undergo further substitution with a sulfonamide $R^2SO_2NH_2$, yielding the desired *N*,*N*′-bissulfonylphosphoramidimidates **6**. Indeed, we found that treating different BINOLs **7** with PCl_5, followed by the addition of $R^2SO_2NH_2$ in hot pyridine, proceeded smoothly to give the corresponding Yamamoto catalysts **2** after hydrolytic workup. Apparently, the second substitution reaction with an additional sulfonamide $R^2SO_2NH_2$ is significantly slower. Fortunately, we found that prolonged heating, and the addition of *N*,*N*-dimethylpyridin-4-amine (DMAP), furnished the desired *N*,*N*′-bissulfonylphosphoramidimidates **6** in a one-pot procedure (Scheme 2).

Our newly developed route[17] tolerates various substituents at the 3,3′-positions of enantiopure BINOL **7** (Scheme 2), including 2,4,6-triisopropylphenyl **8**, 3,5-bis(trifluoromethyl) **9**, naphthalen-1-yl **10**, phenanthren-9-yl **11**, and 3,3″,5,5″-tetrakis(trifluoromethyl)-[1,1′:3′,1′-terphenyl]-5′-yl **12**. Moreover, further modifications at the active center on the NH-acidic nitrogen afforded highly hindered *N*,*N*′-bisarylsulfonylphosphoramidimidates **13** and **14**. The *N*,*N*′-bissulfonylphosphoramidimidates displayed interesting catalytic performances when compared to previously described Brønsted acid catalysts, such as phosphoric acid TRIP (**15**)[18,19] and phosphoramide **16**[10] (Scheme 3).

For example, phosphoramidimidate **8** was found to be significantly more active in catalyzing the diastereoselective addition of trimethylhydroquinone (TMHQ) to isophytol.[20] α-Tocopherol[21] was generated at room temperature after 23 hours, while TRIP (**15**) and phosphoramide **16** did not catalyze the desired transformation even after extensive heating.



Scheme 3 Preliminary exploration on the catalytic performance of phosphoramidimidate Brønsted acids; Tf = SO_2CF_3

In summary, we have designed and developed highly acidic BINOL-derived *N,N′*-bistriflylphosphoramidimidate and *N,N′*-bisarylsulfonylphosphoramidimidate Brønsted acids. Their application in asymmetric Brønsted acid catalysis shows intriguing effects on acidity and reactivity and therefore significantly higher performance compared to previously described phosphoric acid derivatives. Investigations and more detailed studies on these new motif's performances are ongoing in our laboratories.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560971.

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(17) **General Procedure**
In a flame-dried flask under Ar the corresponding (*S*)- or (*R*)-BINOL derivative (1.0 equiv) was dissolved in freshly distilled pyridine (0.10 M), PCl_5 (2.0 equiv) was added, and the mixture was heated to 85 °C until full consumption of the starting material was observed (TLC). The reaction mixture was cooled to r.t. and $CF_3SO_2NH_2$ (12 equiv) and *N,N*-dimethylpyridin-4-amine (DMAP, 0.5 equiv) were added, and the mixture was heated to 85 °C until full consumption was observed (TLC). The reaction mixture was cooled to r.t., and concentrated under reduced pressure. HCl (1.0 M) was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (silica gel), acidification in CH_2Cl_2 with HCl (6.0 M) followed by drying under reduced pressure with toluene afforded the phosphoramidimidates.
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(21) **Experimental Details**
A mixture of TMHQ (5 mg, 0.03 mmol, 1.0 equiv), isophytol (9 mg, 0.03 mmol, 1.0 equiv), and catalyst **8** (2 mg, 1.5 µmol, 0.05 equiv) in CH_2Cl_2 was stirred at 23 °C for 23 h. Et_3N (3 µL) was added, and the mixture was filtered through silica gel and concentrated under reduced pressure. Conversions were determined by ^1H NMR relative to TMHQ followed by purification on silica gel. Diastereomeric ratios (d.r.) were determined by HPLC with a chiral stationary phase (Daicel Chiracel Cellucoat RP column, 1 mL/min, 90:10 MeCN–H_2O, 220 nm, t_R = 4.00 min, t_R = 4.34 min).