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N-Triflylphosphorimidoyl Trichloride: A Versatile Reagent for the Synthesis of Strong Chiral Brønsted Acids

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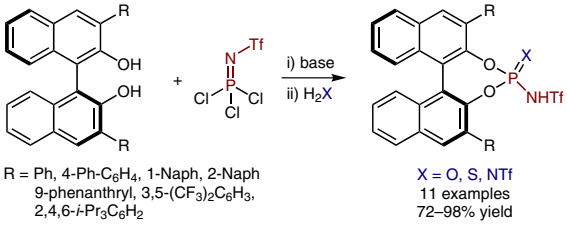

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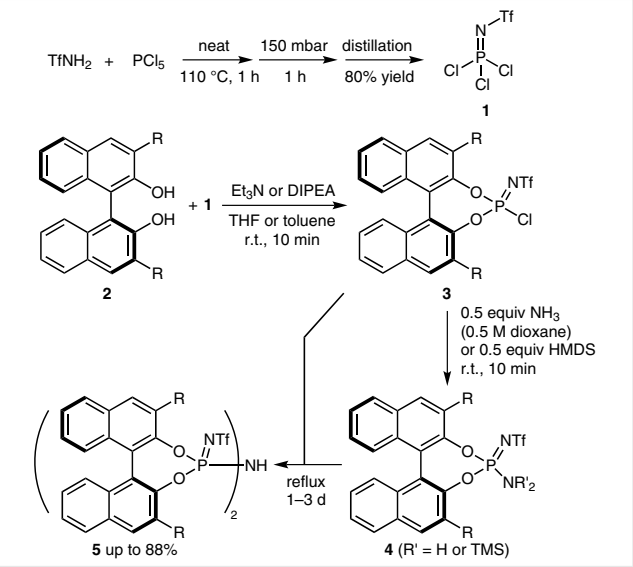
Abstract A series of strong Brønsted acids has been synthesized in high yields using *N*-triflylphosphorimidoyl trichloride as reagent. The syntheses proceed efficiently with electron-rich, electron-deficient, and sterically hindered substrates.

Key words *N*-triflylphosphorimidoyl trichloride, Brønsted acid, *N*-triflylphosphoramide, *N*-triflylthiophosphoramide, *N*,*N*′-bis(triflyl)phosphoramidimidate

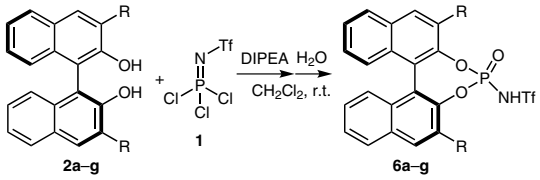
Over the last decade, chiral phosphoric acid catalysts have attracted great attention because of their remarkable reactivity and ease of handling.[1] Since Akiyama and Terada had reported successful application of BINOL-derived phosphoric acids or their salts as catalysts in Mannich reactions, numerous catalyst variations have been developed by modifying the 3,3′-substituents of the BINOL backbone.[2] Furthermore, the Yamamoto group demonstrated that the activity of phosphoric acid catalysts can be enhanced by replacing the OH group with an *N*-triflyl group.[3] Due to the higher acidity of the resulting *N*-triflylphosphoramides, several groups successfully reported asymmetric reactions which could not be accomplished using the original phosphoric acids.[4] However, despite their utility, the synthesis of these catalysts requires a two-step procedure which involves a solvent change and a relatively long reaction time under heating.[3,5] During our studies on the development of even stronger Brønsted acid catalysts, we recently reported a practical method to introduce *N*-triflyl groups to molecular structures using *N*-triflylphosphorimidoyl trichloride (**1**) as a reagent (Scheme 1). We have prepared this substance in a solid-state reaction between phosphorous pentachloride (PCl_5) and trifluoromethansulfonylamide under reduced pressure.[6] When compound **1** was reacted with different BINOLs (**2**) in the presence of triethylamine or diisopropylethylamine in THF or toluene, intermediate **3** was formed within ten minutes. Adding 0.5 equivalent of ammonia or hexamethyldisilazane afforded the corresponding *N*-triflylphosphoramidimidate **4** in situ. With further heating under reflux, novel imidodiphosphorimidates (IDPi) **5** were obtained successively. On the basis of this observation, we wondered if it was possible to establish a new approach to Yamamoto catalysts, simply by hydrolyzing intermediate **3**. Herein we report the fruition of these efforts with a general approach to various *N*-triflyl-substituted chiral Brønsted acids.



Scheme 1 Preparation of *N*-triflylphosphorimidoyl trichloride **1** and its application to the synthesis of imidodiphosphorimidates **5**

Indeed, most BINOLs **2a–f**, upon reaction with reagent **1** in dichloromethane and DIPEA, gave the corresponding intermediate **3** within 10 minutes. With sterically hindered BINOL **2g**, the reaction took 1 hour until completion. Further reaction with water required only 10 minutes with chlorides **3a–f** and 1 hour with compound **3g** to furnish the corresponding acids. Products **6a–g** were obtained in >80% yield regardless of the electronic or steric properties of the BINOL starting material (Table 1).

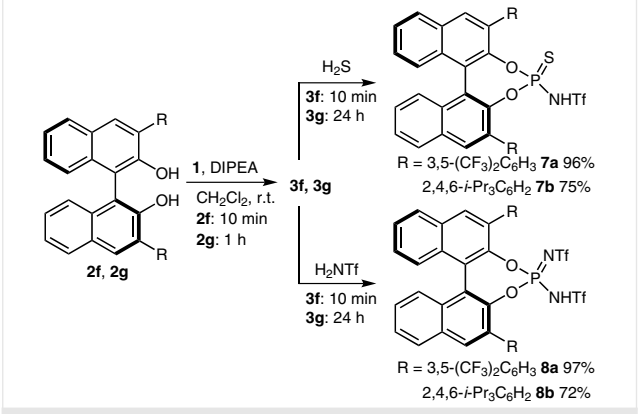
Table 1 Substrate Scope of the Yamamoto-Type Brønsted Acid Synthesis[a]



Entry	Product	Config.	R	Yield (%)
1	**6a**	*S*	Ph	98
2	**6b**	*R*	4-PhC_6H_4	97
3	**6c**	*S*	1-Naph	90
4	**6d**	*R*	2-Naph	96
5	**6e**	*S*	9-phenanthryl	89
6	**6f**	*S*	3,5-$(CF_3)_2C_6H_3$	97
7	**6g**	*S*	2,4,6-*i*-$Pr_3C_6H_2$[b]	82

[a] Reactions were performed with **2** (1.0 equiv), **1** (1.1 equiv), and DIPEA (5.0 equiv) in CH_2Cl_2 (0.25 mL) for 10 min, and then H_2O (20 μL) was added to hydrolyze the intermediates **3**.
[b] In this case, substitution and hydrolysis reactions each took 1 h.

Next, we applied our method to synthesize other strong Brønsted acids (Scheme 2). In 2008, the Yamamoto group exchanged the oxo group of their catalysts with a thio group. The resulting more acidic *N*-triflylthiophosphoramides successfully enabled catalytic enantioselective protonation reactions.[7] Later, our group exchanged the oxo group with an *N*-triflyl imino group expecting an even further increase in acidity.[8] In order to also obtain these two stronger acid motifs, intermediate **3** was reacted with H_2S or with triflamide, respectively. The target acids **7** and **8** were readily obtained within 20 minutes or 1 day, depending on the substrates.



Scheme 2 Synthesis of *N*-triflylthiophosphoramides and *N*,*N*′-bis(triflyl)phosphoramidimidates

In summary, we have established a simple and practical route to synthesize strong chiral Brønsted acids. The method is effective for the preparation of *N*-triflylphosphoramides with electron-deficient, electron-rich, and sterically demanding substrates.[9] Furthermore, both of *N*-triflylthiophosphoramides and *N*,*N*′-bis(triflyl)phosphoramidimidates were prepared in high yields within one day. Further use of reagent **1** in catalyst development is currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588782.

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(9) **General Procedure**: In a flame-dried vial under Ar, the corresponding (*S*)- or (*R*)-BINOL (1.0 equiv) was dissolved in anhyd CH_2Cl_2 (0.20 M). $TfNPCl_3$ (1.1 equiv) and DIPEA (5.0 equiv) were added and the mixture was stirred for 10 min at ambient temperature. After the full consumption of the starting material (as indicated by TLC), the second nucleophile was added (20 µL for H_2O, 2.0 equiv for H_2S and $TfNH_2$). After an additional 10 min of stirring, the reaction mixture was dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel to afford the desired product as a salt. Acidification in CH_2Cl_2 with HCl (3.0 M) followed by drying under reduced pressure afforded the desired product as a free acid.

(10) **Spectroscopic Data of (*S*)-6a**: ^{1}H NMR (501 MHz, CD_2Cl_2): δ = 8.14 (s, 1 H), 8.09 (s, 1 H), 8.05 (dd, *J* = 8.4, 1.1 Hz, 1 H), 8.00 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.67–7.72 (m, 2 H), 7.60 (ddt, *J* = 10.4, 6.0, 1.9 Hz, 3 H), 7.48 (dd, *J* = 8.4, 7.0 Hz, 2 H), 7.39 (m, 7 H), 7.29 (dd, *J* = 8.6, 1.1 Hz, 1 H), 7.22 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1 H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 143.53 (d, *J* = 11.7 Hz), 142.73 (d, *J* = 9.4 Hz), 136.01, 135.98, 133.55, 133.53, 133.36, 133.34, 131.96, 131.93, 131.83, 131.80, 130.00, 129.71, 128.54, 128.53, 128.47, 128.11, 128.09, 127.87, 126.95, 126.94, 126.79, 126.69, 126.62, 126.38, 122.21 (d, *J* = 2.0 Hz), 122.19 (d, *J* = 3.0 Hz), 118.71 (qd, *J* = 322.1, 1.6 Hz). ^{19}F NMR (471 MHz, CD_2Cl_2): δ = –77.8. ^{31}P NMR (203 MHz, CD_2Cl_2): δ = –5.8. HRMS (ESI): *m/z* [M – H$^+$] calcd for $C_{33}H_{20}F_3NO_5PS$: 630.0757; found: 630.0759.