1,1,3,3-Tetratriflylpropene (TTP) – A Strong, Allylic C–H Acid for Brønsted and Lewis Acid Catalysis

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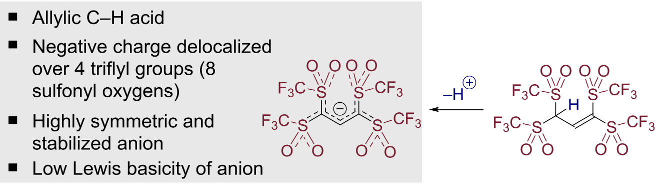
Abstract: Tetratrifylpropene (TTP) has been developed as a highly acidic, allylic C–H acid for Brønsted- and Lewis acid catalysis. It can readily be obtained in two steps and consistently shows exceptional catalytic activities for Mukaiyama aldol, Hosomi–Sakurai, and Friedel–Crafts acylation reactions. X-ray analyses of TTP and its salts confirm its designed, allylic structure enabling the delocalization of the negative charge over four triflyl groups. NMR experiments, acidity measurements, and theoretical investigations provide further insights to rationalize the remarkable reactivity of TTP.

Strong organic acids and their salts are of fundamental importance as charge carriers in fuel cells (e.g. electrolytes), as stabilizers of highly reactive species, and as reagents or catalysts in chemical synthesis.[1] Developing a strong organic acid fundamentally means designing the corresponding anion: its negative charge should be as delocalized as possible to reduce its basicity. The most successful strategy to reducing anion basicity involves the utilization of strongly electron-withdrawing groups,[1a,2] among which the trifluoromethanesulfonyl (triflyl or Tf) group represents a particularly powerful and frequently used one.[3] Introducing triflyl groups to organic molecules imparts an increased acidity to the neighboring α-hydrogens, an effect which is enhanced with the number of triflyl groups. As a result, a maximum amount of triflyl groups often confers highest acidity to a molecule.[3b,4] Examples for strong acids containing triflyl moieties are triflic acid (TfOH),[5] triflimide (Tf_2NH),[6] and tris(triflyl)methane (Tf_3CH)[7] with pK_a values (in dichloroethane, relative to picric acid) of –11.4 (TfOH), –11.9 (Tf_2NH), and an estimated –16.4 (Tf_3CH).[1b] Triflimide and to a lesser extent also tris(triflyl)methane have been employed in Lewis- and Brønsted acid catalysis, either in their protonated form, silylated, or as salts.[8,9] The observed pK_a trend is remarkable, as C–H bonds are often intrinsically unpolarized and proton dissociation is usually less facile than that of O–H and N–H bonds. However, as the tetravalency of carbon allows the introduction of up to three electron-withdrawing groups, a higher delocalization of the negative charge is achieved resulting in a higher acidity when compared to O–H and N–H acids.

To increase the number of electron-withdrawing groups beyond three, vinylogous acids can be designed and synthe-sized. Inspired by the work of R. Kuhn and others,[10,11] we were intrigued in assessing an allylic C–H acid carrying four triflyl groups resulting in the design and development of tetratriflylpropene (**TTP**, Scheme 1), which we present herein.



Scheme 1. Design of tetratriflylpropene (**TTP**).

The anion of **TTP** was designed to be highly symmetric such that the negative charge can be delocalized over four triflyl groups each containing two oxygens (leading to an overall number of eight, conjugated oxygen atoms). In comparison to Tf_3CH, the scaffold of our allylic C–H acid is expanded by two carbon atoms. The four CF_3 groups of **TTP** are also presumed to stabilize the anion through their field-inductive properties. The high stabilization of the anion should minimize its Lewis basicity thereby limiting protonation and coordination to Lewis acids and increase the Brønsted acidity of **TTP**.

In analogy to our previous synthesis of chiral allyltetrasulfones,[12] **TTP** can be readily obtained via a two-step synthesis (Scheme 2) starting from commercially available bistriflylmethane (**1**).

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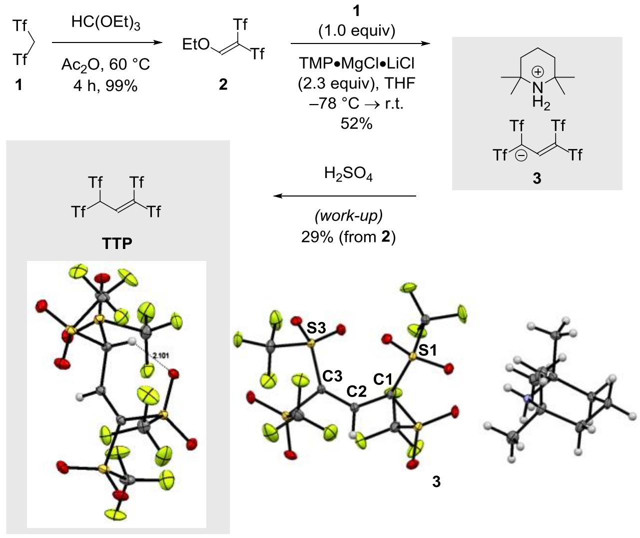
CCDC1509165, 1509166, and 1509167 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.



Scheme 2. Synthesis of **TTP** and X-ray analysis.

Disulfone **1** is first converted essentially quantitatively to enolether **2**,[12] which is then treated with bistriflylmethane (**1**) and TMP base (= 2,2,6,6-tetramethylpisolution) to give the TMP•TTP salt (**3**). While ammonium salt **3** could be conveniently isolated, finding suitably acidic conditions to obtain pure and reasonable quantities of **TTP** proved to be rather challenging. All tested aqueous acids and many organic acid solutions gave none or only traces of **TTP**. Finally, we found that satisfying amounts of clean **TTP** could be obtained upon work-up with pure concentrated sulfuric acid. Isolated in pure form, **TTP** is very hygroscopic and readily decomposes in the presence of water. Both, salt **3** and **TTP**, could successfully be crystallized and their crystal structures are shown as ORTEP drawings (Scheme 2). Remarkably, **TTP** showed an intramolecular hydrogen bond between the acidic proton and a neighboring sulfonyl group with an average length of 2.13 Å. The average angle between C,H and O is 133°. Both values lie within the expected range for typical H–bonds.[13] The crystal structure of TTP•TMP (**3**) showed that not all four triflyl groups are in the same plane. This structural property may reduce the stability of the anion, potentially compromising the acidity of **TTP**. Besides this, the triflyl groups in the 1,3 positions seemed to be slightly bent away from each other as the angles between S3,C3, and C2 and C2,C1, and S1 had an average value of 124° (instead of 120°). This bending might be caused by the charge repulsion between partially negatively charged oxygens. When the tetraethylammonium salt of **TTP** was crystallized and analyzed via X-ray structural analysis (see Figure S3 of SI) an average angle of 130° was measured for the same atoms indicating an even stronger bending.

To evaluate the catalytic properties of **TTP** in silylium-based Lewis-acid catalysis, the Mukaiyama aldol reaction of TBS-protected silyl ketene acetal **5** with benzophenone (**4**) was chosen as a model reaction (Figure 1).[14] This aldol reaction is challenging as ketones are generally less reactive than aldehydes and possibly also due to the required transfer of the rather bulky *tert*-butyldimethyl silyl group to give silyl ether **6**. Triflimide (**8**), tris(triflyl)methane (**7**), and the structurally related carbon acid **9**,[15] which can be viewed as an unconjugated/hydrogenated version of **TTP**, were chosen as benchmark acids. The reaction was monitored by ReactIR in order to compare product formation at different time points.

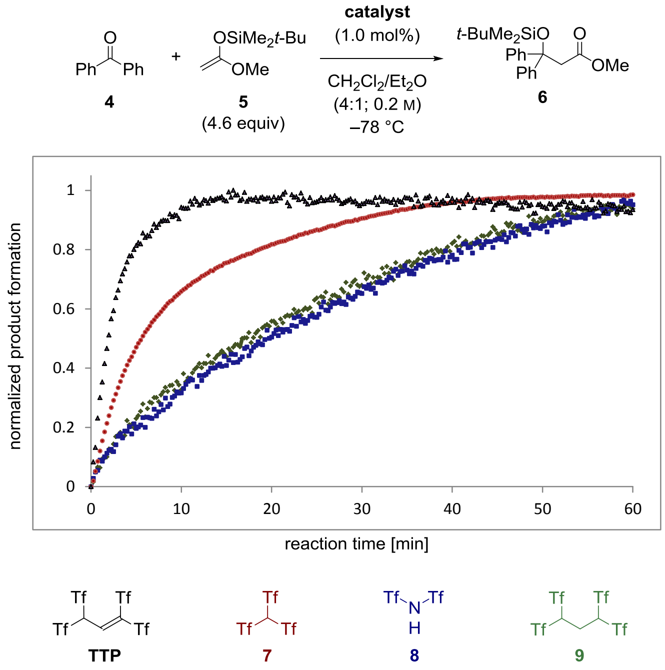
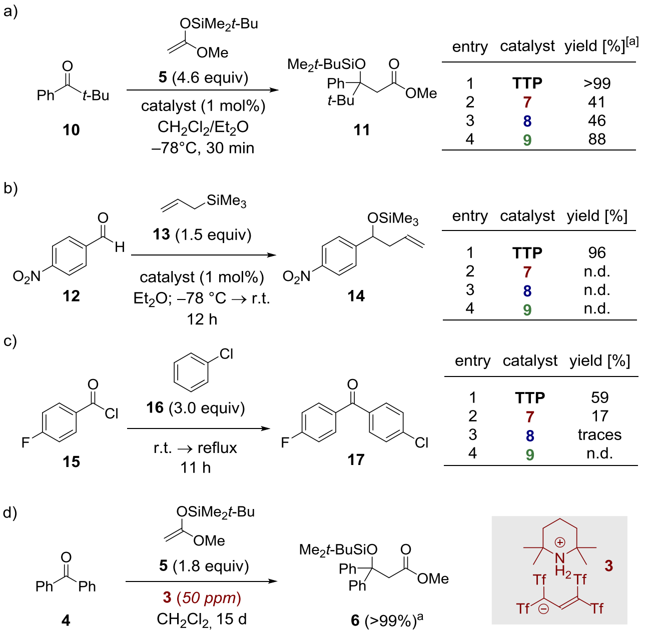


Figure 1. Comparing catalytic Mukaiyama aldol reactions using ReactIR. For all reactions 1 mmol of ketone **4** was employed and the reaction was halted by the addition of MeOH and Et_3N.[16] The reaction was carried out three times per catalyst and product formation was measured in situ by ReactIR. Triphenylmethane was added as an internal standard and full product formation was verified by ^1H NMR analysis. A representative plot for each catalyst is shown which is closest to the average of the three ReactIR measurements.

Remarkably, **TTP** showed the highest reaction rate with 90% product formation after only 7 min, followed by C–H acid **7** with 28 min. Catalysts **8** and **9** showed an almost identical reaction rate with an average of 50–52 min to reach 90% product formation.

After these promising initial results for **TTP** catalysis, other reactions were targeted to further evaluate its activity in Lewis- and Brønsted acid catalysis (Figure 2). For the previously undescribed Mukaiyama aldol addition of ketene acetal **5** to the sterically more demanding ketone **10**, **TTP** again proved to be the most active catalyst (Figure 2a). Catalyst **9** also displayed a relatively high activity when compared to catalysts **7** and **8**, which performed similarly. The high reactivity of bis-C–H acid **9** is somewhat unexpected, as it displayed lower activity than tris(triflyl)methane (**7**) in the Mukaiyama aldol reaction of nucleophile **5** with benzophenone (Figure 1). Reports from the Taguchi group[15b,15c] already disclosed carbon acid **9** as a more effective catalyst of a vinylogous Mukaiyama–Michael reaction than Tf_2NH (**8**). These experimental findings may be partially rationalized as **9** is a diacid, which could in principle lead to a doubly silylated, catalytically active species.[15c] The reported crystal structure of diacid **9** showed two intramolecular hydrogen bonds between the acidic protons and oxygen atoms of one of the opposing triflyl groups, respectively.[15c] These hydrogen bonds may be strengthened upon deprotonation suggesting the alternative possibility of a Brønsted acid assisted Lewis acid mechanism of acid **9**.



entry	catalyst	yield [%][a]
1	**TTP**	>99
2	**7**	41
3	**8**	46
4	**9**	88

entry	catalyst	yield [%]
1	**TTP**	96
2	**7**	n.d.
3	**8**	n.d.
4	**9**	n.d.

entry	catalyst	yield [%]
1	**TTP**	59
2	**7**	17
3	**8**	traces
4	**9**	n.d.

Figure 2. Application of **TTP** and comparison with other catalysts. All reactions were run on 1 mmol scale (with regard to starting material **10**, **12**, and **15**) except d) which was run on a 10 mmol scale. Reaction a) was quenched via the addition of MeOH and Et_3N and reaction b) was quenched via the addition of Et_3N. For reaction b) and c) yields refer to isolated products. Product **14** was isolated as free alcohol by flash chromatography. [a] Triphenylmethane was added to reaction a) and d) and the yield was determined by ^1H NMR analysis. n.d. = not detected. For reaction a) a previously reported chiral binaphthyl-allyl-tetrasulfones (BALT) C–H acid (substituted with a phenanthrenyl moiety)[12] was also tested but no product could be obtained.

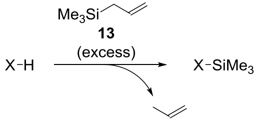
The Hosomi–Sakurai reaction[17] of electron-poor *p*-nitrobenzaldehyde (**12**) with allylsilane **13** was chosen as a challenging example of another class of synthetically useful C–C bond forming reaction (Figure 2b).[18] Due to the nitro group in the *para* position of **12**, the Lewis basicity of the aldehyde is reduced rendering the activation via the coordination of a Lewis acid to the carbonyl lone pair of aldehyde **12** unfavorable. Remarkably, only **TTP** was found to be active under these conditions and gave the corresponding silyl ether **14** in almost quantitative yield, while all other tested catalysts gave no reaction under these conditions.[19]

In addition, the difficult Brønsted acid catalyzed Friedel–Crafts acylation reaction of electronpoor chlorobenzene (**16**) with benzoylchloride **15** was carried out in the presence of the different catalysts (Figure 2c).[20] When catalysts **8** and **9** were employed, no desired product could be isolated. Carbon acid **7** was able to give 17% of product, while **TTP** gave a satisfying 59% yield, illustrating its potential in Brønsted acid catalysis.

Remarkably, ammonium salt **3** was also able to catalyze the Mukaiyama aldol reaction of silyl ketene acetal **5** with benzophenone (**5**) at a very low catalyst loading of 50 ppm (0.005 mol%) at room temperature (Figure 2d).

During the application of **TTP** to acid catalyzed reactions, we became more and more interested in elucidating its acidity. The well-established concept of fluoride ion affinity (FIA) to computationally access Lewis acidities already proved to be insightful for other strong organic acids.[14a,21] Therefore, we used this approach to calculate the FIA values of the catalytically employed silicon-centered Lewis acids (Table 1). The FIA calculations suggest silylated **TTP** as the strongest Lewis acid. Our calculations also confirm catalyst **7** as the second most active species. The two computationally predicted least active catalysts **8** and **9**, although structurally very different, were found to have very similar activities in our experimental studies. The Mukaiyama aldol reaction of **10** with **11** (Figure 2a) constitutes a notable exception to this good agreement between theoretical and experimental results, as a remarkably high activity of carbon acid **9** was observed in this case, presumably due to the different mode of action of this bifunctional catalyst in this specific case.

Table 1. Fluoride ion affinities (FIA) of silyl-Lewis-acids and ^{29}Si shifts Table.

			**FIA (H in kcal/mol)[a]**	**FIA (U in kcal/mol)[b]**
Entry	**X**	**Me_3SiX [$\delta(^{29}Si)$] [ppm]**		
1	**TTP**	67.2	118.1	89.5
2	**7**	66.6	108.7	85.2
3	**8**	65.7	96.2[14a]	76.2[14a]
4	**9**	52.5	106.0	80.9

[a] BP86/SVP, 298.15 K, 1 bar. [b] kcal/mol, BP86/SVP, in CH_2Cl_2. ^{29}Si shifts were determined in a mixture of $CDCl_3$ and D-Et_2O (4:1).

In order to complement our theoretical data, ^{29}Si NMR shift experiments were conducted next. Although this approach was reported to have limited correlation with Lewis acidities and catalytic activities,[21d] we attempted to corroborate our theoretical data with these studies. Each catalyst was treated with allyltrimethylsilane (**13**) in a deuterated solvent mixture and ^1H as well as ^{29}Si NMR spectra were acquired. Different chemical shifts for the ^{29}Si NMR signal were detected for each catalyst. A less Lewis basic catalyst anion should provide a more Lewis acidic and deshielded silylium ion equivalent, resulting in a more downfield signal in the ^{29}Si NMR spectrum. **TTP** provided the most downfield signal, thereby confirming its exceptional Lewis acidity. However, the absolute differences (in ppm) to acids **7** and **8** were relatively small. Surprisingly, diacid **9** provided by far the least downfield signal which may once again hint at a different activation mode for this catalyst. The small differences between **TTP** and acids **7** and **8** can be explained with the diethyl ether solvent, which may coordinate to the silylium ion, decreasing its overall Lewis acidity and resulting in a less downfield chemical shift in the ^{29}Si NMR spectra for all catalysts.

In addition, a pK_a value (relative to picric acid) for **TTP** was determined in dichloroethane as –15.4 and a pK_a estimate in acetonitrile (on the basis of correlation)[1b] is –2.8. Overall, the obtained results are in good agreement with our experimental findings: the acidity of triflimide (**8**) is by over 3 orders of magnitude and the acidity of carbon acid **9** (pK_a = –5.2) is by at least 9 (approximate) orders of magnitude lower than that of **TTP**. However, the acidity order of **TTP** and Tf$_3$CH (**7**), when compared to the previously estimated pK_a value of –16.4,[1b] is the opposite to their order of catalytic activity.

In conclusion, we report the synthesis, structure, applica-tion, and experimental and theoretical evaluation of **TTP**, which is a novel, allylic C–H acid showing exceptionally high reactivity in Lewis- and Brønsted acid catalyzed reactions. Our catalyst can readily be obtained in two steps from commercially available bistriflylmethane. The structures of its protonated form as well as its salts were solved using X-ray analysis. In comparison to the prominent, very active, organic acids **7**, **8**, and **9**, **TTP** consistently displayed the highest activity. This outstanding activity of **TTP** could be corroborated through FIA calculations, relative pK_a measurements and ^{29}Si shift experiments. We anticipate that **TTP** as a strongly acidic, allylic C–H acid will enable the catalysis of a variety of challenging reactions, which are currently being studied in our laboratories. We furthermore envisage that **TTP** could prove to be useful for applications beyond organocatalysis, such as in electrolytes, ionic liquids, or as weakly coordinating anion.

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Keywords: tetratriflylpropene • allylic C–H acids • strong acid design • Brønsted- and Lewis acids

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