

Super Brønsted Acid Catalysis in Organic Synthesis

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Abstract: This mini-review concerns the rapidly growing field of Brønsted acid catalysis. Brønsted acid catalysts are able to play an important role in green chemistry. Without the use of any transition metal catalysts, various organic transformations including asymmetric synthesis can be performed efficiently. This review summarizes our recent results in this field.

Keywords: Aldol · Allylation · Diels–Alder · Super Brønsted acid · Super silyl group

1. Introduction

Two acid–base definitions are used in organic chemistry today: The Brønsted–Lowry definition and the Lewis definition. The Brønsted–Lowry definition refers to substances that either donate protons (acid) or accept protons (base). The Lewis definition refers to electron acceptors (acid) and electron donors (base). The term ‘super Brøn-

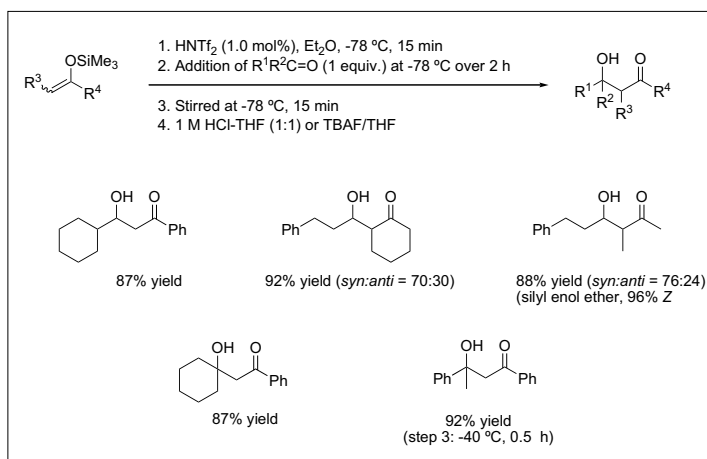
sted acid’ was described by Gillespie as Brønsted acids stronger than 100% sulfuric acid.^[1] While acids of this strength can be detrimental to common reaction conditions, many of these super acids have found great use as catalysts in organic synthesis.

2. HNTf₂ as a Catalyst/Initiator

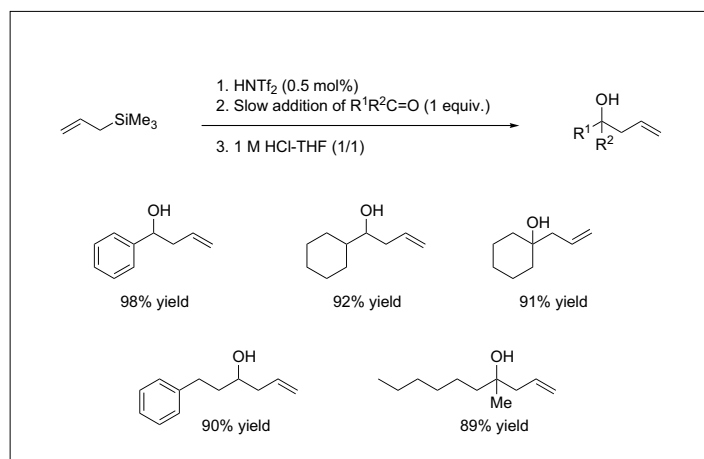
One example of the high utility of these reagents has been demonstrated by the simple Mukaiyama aldol reaction as shown in Scheme 1.^[2] This system was also applied to the Sakurai–Hosomi allylation of ketones and aldehydes (Scheme 2). Although the real catalyst in these reactions is not the Brønsted acid itself, but rather Me₃SiNTf₂, the high reactivity of this acid catalyst comes from the high reactivity of Tf₂NH and more importantly the stability of the counter anion, NTf₂⁻.

Related to the aforementioned silyl Lewis acid catalysis, Brønsted acids and silyl Lewis acid catalysts are often inextricably linked (the Brønsted acid can be termed initiator in many cases). This comes from the facile generation of the silyl Lewis acid from super Brønsted acid and silyl enol ether (or allylsilane) through protodesilylation (Scheme 3). Since Me₃SiNTf₂ is a reactive species and moisture-sensitive reagent, small amounts of water in the reaction mixture would cause decomposition to give Me₃SiOH and HNTf₂. The silanol, Me₃SiOH, that is generated will then react with Me₃SiNTf₂, and provide inert Me₃SiOSiMe₃ and HNTf₂. The regenerated HNTf₂ will readily react with allyltrimethylsilane (or silyl enol ether in Mukaiyama aldol reactions), and provide Me₃SiNTf₂ again. The repetition of this cycle should produce strictly anhydrous conditions. Thus this catalytic cycle constitutes a self-repairing system for Lewis acid catalysis and may

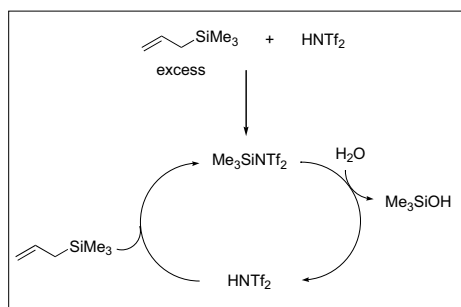
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Scheme 1. HNTf₂-initiated Mukaiyama aldol reaction



Scheme 2. Sakurai–Hosomi allylation of ketones and aldehydes

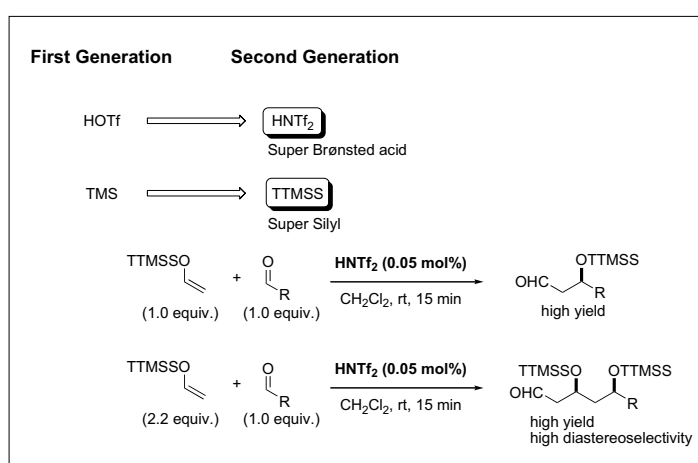
Scheme 3. Self-repair mechanism of HNTf₂

help explain why particularly low catalyst loading is possible (*i.e.* 0.05 mol% in some cases).

The trimethylsilyl (TMS) group is a widely used protecting group and Lewis acid, as well as an important functional group in many substrates. For these reasons we deemed the TMS group a *first-generation* silyl group. We have recently described that the use of HNTf₂ as a catalyst initiator is very effective for the aldehyde cross-aldol reaction.^[3] Due to the reactivity with HNTf₂ that was not attainable with the classic super Brønsted acid, HOTf, we classified HNTf₂ as a 2nd generation super Brønsted acid (Scheme 4). The success of this reaction proved to be the use of triflimide as the catalyst/initiator as well as the use of tris(trimethylsilyl)silyl (TTMSS) enol ethers. The use of the TTMSS group, also referred to as the super silyl group, is one of the keys for this reaction and its unique reactivity caused us to consider it as a *second-generation* silyl group.

The exceptional diastereoselectivity, 'control' and reactivity of the TTMSS group can be attributed to the two classic arguments of sterics and electronics. The TTMSS group is extraordinarily bulky and has been stated to shield molecular skeletons effectively.^[4] After the first addition and silyl transfer, the steric encumbrance of this group is likely to kinetically slow down the addition of a second equivalent of nucleophile to a rate that does not compete with the rate of the first addition. When all of the aldehyde starting material has been consumed, a second addition occurs giving the 2:1 (silyl enol ether:aldehyde starting material) adducts with high diastereoselectivity (Scheme 4).

Intrigued by TTMSSNTf₂ catalysis, we used ²⁹Si NMR as an indicator of silicon Lewis acidity and found that the central silicon of TTMSSNTf₂ was shifted significantly down-field (>6 ppm) compared to TMS- and TBSNTf₂, and only slightly down-field from pentamethyldisilane-NTf₂ (62.2, 55.9, 55.5, and 60.8 ppm respectively). This trend shows a considerable difference in the cationic nature of silyl groups with only silicon-carbon bonds *versus* those with silicon-silicon bonds.



Scheme 4. Use of second-generation super Brønsted acid and second-generation silyl group for unprecedented aldehyde-cross-aldol reaction

3. Homogeneous and Heterogeneous Carbon-based Super Brønsted Acids

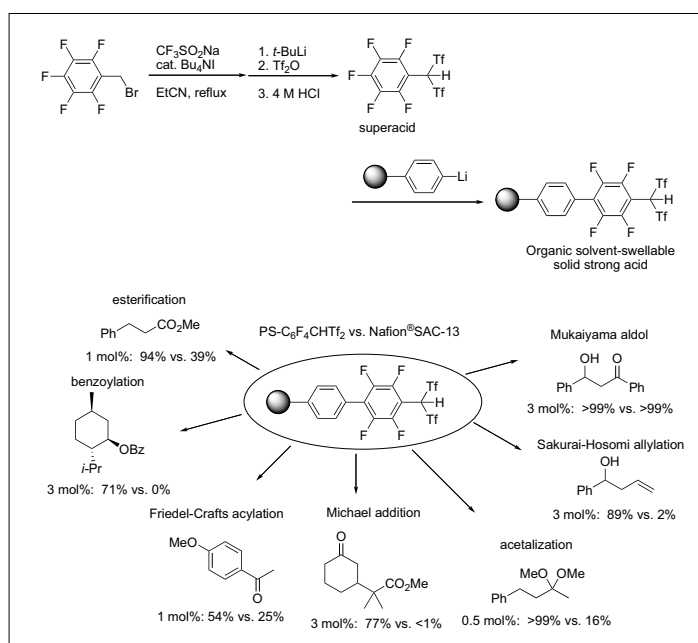
The trifluoromethanesulfonyl (triflyl, Tf) group is one of the strongest neutral electron-withdrawing groups. In particular, it greatly increases the acidity of hydrogen atoms at α -positions. The steric and electronic factors of the aromatic ring on arylbis(triflyl)methanes are expected to greatly influence the Brønsted acidity, catalytic activity, and selectivity for organic reactions. We have developed new strong carbon Brønsted acids, pentafluorophenylbis(triflyl)methane and polystyrene-bound tetrafluorophenyl-bis(triflyl)methane (Scheme 5).^[5] The synthesis of the resin-bound Brønsted acid has been accomplished by using the nucleophilic *para*-substitution reaction of lithium pentafluorophenylbis(triflyl)methide with lithiated polystyrenes as a key step. This is the first example of a highly acidic heterogeneous Brønsted acid catalyst that is effectively swollen by non-polar organic solvents, and its catalytic activities are superior to those of Nafion[®] SAC-13.

4. Reversal of Chemoselectivity from HNTf₂ to B(C₆F₅)₃

In 2005 a very interesting result in the Diels-Alder reaction catalyzed by HNTf₂ or Lewis acids (*i.e.* B(C₆F₅)₃) was found.^[6] The use of the Lewis acids provided the Diels-Alder products of α,β -unsaturated aldehydes and dienes selectively, while HNTf₂ gave the Diels-Alder adduct of α,β -unsaturated ketones and dienes preferentially (Table 1). The selectivity is believed to arise from a combination of steric as well as electronic effects of the dienophiles (Fig.).

5. Synthesis and Application of a Chiral Brønsted Acid

Metal-free chiral Brønsted acid catalysts have recently emerged as a new class of chiral catalysts. Several nice chiral Brønsted acids such as urea/thiourea, alcohols, and phosphoric acids have already been reported as chiral catalysts for a variety of



Scheme 5. Synthesis and utility of polystyrene-bound tetrafluorophenylbis(triflyl)methane

Table 1. Reversal of chemoselectivity between HNTf₂ and B(C₆F₅)₃

entry	Diene	Conditions	Catalyst [mol%]	Yield [%], Ratio of A:B
1		-78 °C, 1 h	Tf ₂ NH (5)	86, 12:88
2		-96 °C, 1 h	Tf ₂ NH (5)	93, 5:95
3		-78 °C, 1 h	B(C ₆ F ₅) ₃ (50)	88, 85:15
4		-40 °C, 2 h	Tf ₂ NH (5)	64, 39:61
5		-40 °C, 2 h	B(C ₆ F ₅) ₃ (30)	85, 94:6
6		-40 °C, 2 h	Tf ₂ NH (5)	81, 19:81
7		-40 °C, 2 h	B(C ₆ F ₅) ₃ (30)	75, 95:5
8		-40 °C, 4 h	Tf ₂ NH (5)	51, 22:78
9		-40 °C, 4 h	B(C ₆ F ₅) ₃ (30)	62, 91:10

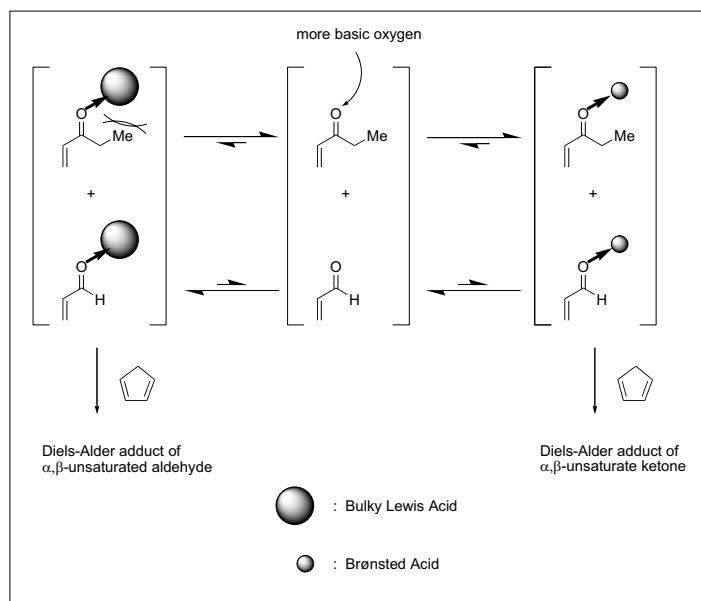


Fig. Rationale for reversal of chemoselectivity based on size of acid catalyst

carbonyl and imine compounds. However, compared with chiral *metal* Lewis acid catalysts, the utility of these chiral Brønsted acid catalysts is still limited to reactive substrates. This drawback can be overcome by designing the Brønsted acid to have higher acidity, which in turn is one of the most important yet challenging tasks for Brønsted acid chemistry. In order to increase the acidity of Brønsted acids, it is necessary to increase the stability of the counter anion. We expected that strong chiral Brønsted acids could be obtained by introduction of a =NTf group into a phosphoric acid moiety. We succeeded in preparing this chiral super Brønsted acid catalyst which is able to catalyze the asymmetric Diels-Alder reaction with α,β -unsaturated ketones (Table 2).^[7] This highly acidic Brønsted acid is capable of catalyzing the title reaction with only 5 mol% loading, which is a relatively low catalyst loading for a chiral organic Brønsted acid.

6. Conclusions and Outlook

The usefulness of the triflyl (Tf) group, specifically in -NTf₂ and RHC(Tf)₂, has been demonstrated in this review. Many of the compounds containing these groups can be considered super Brønsted acids. These super Brønsted acids are capable of catalyzing important organic transformations previously only attainable with sometimes expensive and toxic metals. The application of these types of acids in a catalytic asymmetric platform has also been studied and progress towards a widely applicable chiral Brønsted acid catalyst is still being developed.

Table 2. Diels-Alder reaction with chiral Brønsted acid

Entry	SiR ₃	R ¹	Yield [%]	ee [%]
1	TBS	Me	43	92
2	TIPS	Me	95	92
3	TIPS	H	43	88
4	TIPS	Bn	>99	85
5	TIPS	(4-TBSOC ₆ H ₄)CH ₂	>99	92
6	TIPS	(4-MOMOC ₆ H ₄)CH ₂	>99	87
7	TIPS	(4-HOC ₆ H ₄)CH ₂	35	82
8	TIPS	BzOCH ₂ CH ₂	>99	91

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