Efficient Brønsted Acid Catalyzed Hosomi–Sakurai Reaction of Acetals

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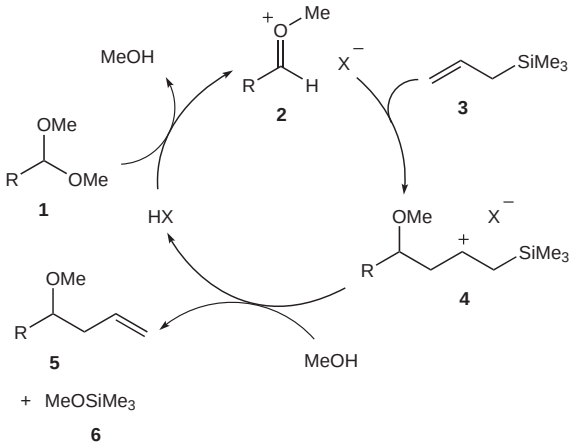
Abstract: Acetals react with allyltrimethylsilane in the presence of a catalytic amount of sulfonic acids to give the corresponding homoallylic ethers in high yields. The scope of the reaction is broad and both aromatic as well as aliphatic acetals can readily be used.

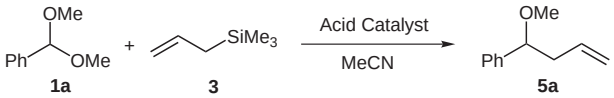
Key words: Hosomi–Sakurai reaction, acetals, organocatalysis, Brønsted acid catalysis, allylsilanes

Acetals are useful intermediates in organic synthesis and undergo coupling reactions with different nucleophiles via carbon–carbon bond formation. Successfully used nucleophiles include silyl enol ethers, allyl transfer reagents, vinyl ethers, and also common olefins as well as cyanide sources. A valuable example is the Hosomi–Sakurai reaction[1] of acetals with allyltrimethylsilane,[2] which furnishes homoallylic ethers. Catalysts that have been employed for this transformation include Lewis acids such as $NbCl_5/AgClO_4$,[3] $AlBr_3/CuBr$,[4] $FeCl_3$,[5] TMSOTf,[6] $Bi(OTf)_3$,[7] $Sc(OTf)_3$,[8] $BiBr_3$,[9] $TMSNTf_2$,[10] $TMSN(SO_2F)_2$,[11] $TiCp_2(CF_3SO_3)_2$,[12] montmorillonite,[13] trityl perchlorate,[14] diphenylboryl triflate,[14] and TMSI.[15] Alternatively, stoichiometric Lewis acidic activators that have been used include $TiCl_4$,[16] $AlCl_3$,[17] $BF_3{\cdot}Et_2O$,[17,18] liquid SO_2,[19] and CuBr/microwave.[20] Several of these methods suffer from drawbacks such as the involvement of compounds that are corrosive, difficult to handle, expensive, or toxic. Others require strictly anhydrous conditions or less practical reaction temperatures. Surprisingly, Brønsted acids have not been studied for this important reaction despite their great potential as easily tunable, economic, and environmentally acceptable catalysts.[21,22] We reasoned that a catalytic cycle could be readily initiated via the reaction of a strong Brønsted acid (HX) with an acetal (**1**) to give an oxonium ion (**2**). Its reaction with allyltrimethylsilane (**3**) would lead to the silicon-stabilized carbocation (**4**). This intermediate in turn should readily collapse to the desired product (**5**) and volatile methoxytrimethylsilane (**6**) upon reaction with methanol, generated in the initializing step of the catalytic cycle (Scheme 1).[23]



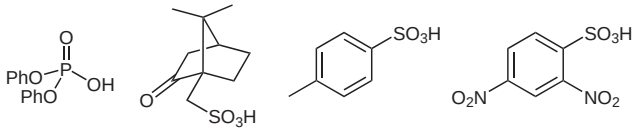
Scheme 1

Table 1 Catalyst Screening for the Allylation of Acetal **1a**



Entry	Acid catalyst	Amount (mol%)	Temperature	Time (h)	Conversion[a] (%)
1	PPA	10	r.t.	21	20
2	PPA	10	60 °C	21	25
3	TFA	10	r.t.	3	>99
4	TFA	5	r.t.	21	60
5	CSA	10	r.t.	24	40
6	*p*-TsOH	10	r.t.	12	>99
7	*p*-TsOH	3	r.t.	15	>99
8	H_2SO_4	2	r.t.	2	95[b]
9	DNBA	2	r.t.	2	>99

[a] Conversion was determined by GC.
[b] By-products were formed.



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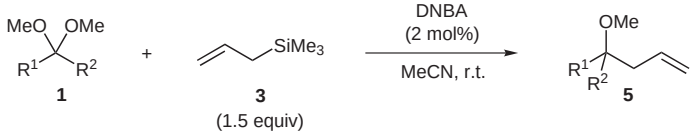
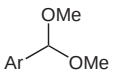
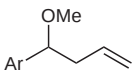
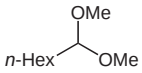
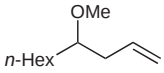
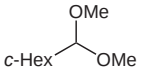
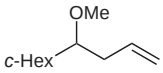
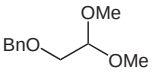
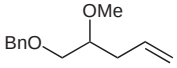
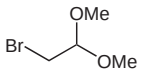
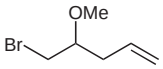
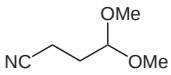
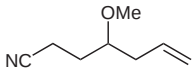
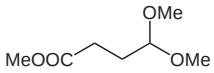
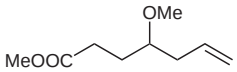
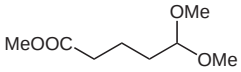
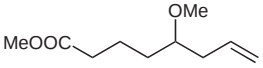
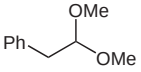
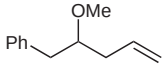
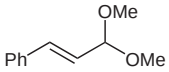
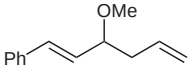
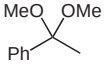
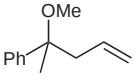
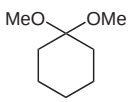
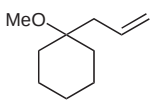
With this reaction design in mind, we have studied several different Brønsted acids for the reaction of benzaldehyde acetal **1a** with allylsilane **3** to give homoallylic ether **5a** (Table 1). In initial experiments, acetonitrile was found to be the best solvent. While the modestly acidic diphenyl phosphate) (PPA) gave some conversion (entries 1 and 2), stronger acids such as trifluoroacetic acid (TFA; entries 3 and 4) and in particular sulfonic acids as well as sulfuric acid (entries 5–9) proved to be much more useful. Dinitrobenzenesulfonic acid (DNBA) turned out to be a powerful catalyst for the reaction. Compared to sulfuric acid, which is also an active catalyst, it mediates the allylation very cleanly without by-product formation and was therefore chosen for further studies. Lowering the catalyst loading from 2 mol% to 1 mol% significantly reduced the turnover and increasing the temperature did not result in any improvement. Consequently, 2 mol% of DNBA was used in subsequent experiments.

After identifying an active catalyst and suitable reaction conditions, we have explored the scope of the reaction

Table 2 Substrate Scope of the Brønsted Acid Catalyzed Hosomi–Sakurai Reaction of Acetals

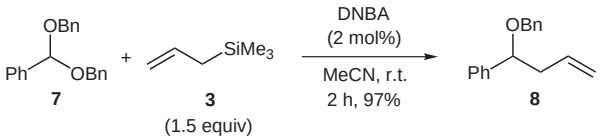


Entry	Acetal	Product	Time (h)	Yield (%)
				
1	Ar = Ph		1	99
2	Ar = *p*-BrC_6H_4		1	95
3	Ar = *p*-$MeOC_6H_4$		2	90
4	Ar = *p*-$O_2NC_6H_4$		3	93
5			2	84
6			2	87
7			7	96
8			8	53[a]
9			7	64[a]
10			3	85
11			3	88
12			1	78
13			2	87
14			1	82
15			2	91

[a] Reduced yield due to volatility of the product.

(Table 2). Upon treating acetals **1** with 1.5 equivalents of allyltrimethylsilane (**3**) in the presence of 2 mol% of DNBA at room temperature in acetonitrile, the corresponding homoallylic ethers **5** were obtained in high yields. It turned out that the selected reaction conditions are broadly useful for a variety of different substrates. Both aromatic acetals (entries 1–4) with electron-rich or electron-poor aryl substituents, as well as simple unbranched or branched aliphatic acetals (entries 5 and 6) can be used with similar efficiencies. Functional groups that are tolerated include a benzyl ether (entry 7), an alkyl bromide (entry 8), a nitrile (entry 9), two esters (entries 10 and 11), and an α,β-unsaturated acetal. Remarkably, even ketone-derived acetals ('ketals') can be employed with good results (entries 14 and 15). The reactions are generally clean and chemoselective and possible products of hydrolysis or aldolization were not detected in the crude mixture. The best result was achieved with benzaldehyde acetal (entry 1), which provided the corresponding homoallylic ether in nearly quantitative yield after only one hour. While in almost all cases full conversion to the desired product was obtained after 2 to 3 hours, the allylation of the bromo (entry 8) as well as the cyano (entry 9) substituted aliphatic acetals was less efficient (85% conversion according to GC after 8 hours and 7 hours, respectively). In addition, the volatility of the corresponding ethers contributed to the moderate isolated yields (53% and 64%) in these cases. It has been reported that the Hosomi–Sakurai reaction of cinnamaldehyde dimethyl acetal with allyltrimethylsilane mediated by stoichiometric amounts of $TiCl_4$ gave only the diallylated product.[16] In contrast, we did not observe any diallylated compound. Although the allylation of cinnamaldehyde acetal has been expected to give a mixture of regioisomeric products resulting from either direct or vinylogous nucleophilic attack of the presumed oxonium ion, DNBA catalyzes the formation of the homoallylic ether regiospecifically (entry 13). Compared to the present Hosomi–Sakurai reaction of acetals, the allylation of benzaldehyde under the same conditions was found to be extremely slow. Even after 21 hours less than 20% of the corresponding homoallylic silyl ether was formed.

Finally, a benzyl acetal (**7**) has also been studied. Subjecting acetal **7** to our reaction conditions provided the synthetically useful benzyl homoallylic ether **8** in good yield (Equation 1).



Equation 1

In summary, we have developed a highly efficient Brønsted acid catalyzed allylation of acetals using allyltrimethylsilane. Significant advantages of our process include: a) its high yields, b) its broad scope, allowing for the use of both aromatic and aliphatic substrates c) its high tolerance towards diverse functional groups, d) its simplicity and practicability, e) its use of an inexpensive and non-toxic Brønsted acid, and f) its low catalyst loading. We are currently extending this methodology to alternative variants and substrate classes.

General Procedure for the Hosomi–Sakurai Reaction

Acetal **1** (1.5 mmol, 1.0 equiv) and allyltrimethylsilane (**3**; 0.36 mL, 2.25 mmol, 1.5 equiv) were added to a solution of DNBA (8.5 mg, 0.03 mmol, 0.02 equiv) in anhydrous MeCN and stirred at r.t. for 1–8 h. The mixture was poured into brine (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The homoallylic ether **5** was isolated by flash chromatography (SiO_2, pentane–Et_2O).

Acknowledgment

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(23) As suggested by a reviewer, the reaction may also be promoted by the in situ generated TMS sulfonate. For an example, see ref. 22a.