Brønsted Acid-Catalyzed Three-Component Hosomi–Sakurai Reactions

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Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday.

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Abstract: Aldehydes react with silyl ethers or the corresponding alcohols and allylsilanes in the presence of catalytic amounts of 2,4-dinitrobenzenesulfonic acid (DNBA) to provide a wide range of homoallylic ethers in moderate to high yields.

Keywords: allylation; Brønsted acids; homoallylic ethers; Hosomi–Sakurai reaction; multicomponent reactions; organocatalysis

Homoallylic ethers represent valuable organic intermediates, which are amenable to further synthetic manipulations. Accordingly, their preparation has attracted considerable attention. The allylation of acetals (1) is a useful method to generate homoallylic ethers (4) and can be mediated by several Lewis acids (a, Scheme 1). However, many acetals are not commercially available and have to be synthesized from the corresponding aldehydes (2). In addition, most of these Hosomi–Sakurai reactions^[1] give rise to homoallyl methyl ethers bearing a protecting group that requires harsh conditions to be cleaved.



Scheme 1. a) Acid-catalyzed Hosomi–Sakurai reaction of acetals; b) acid-catalyzed three-component Hosomi-Sakurai reaction.

Alternatively, a direct approach to homoallylic ethers (4) involves the combination of an aldehyde (2) with a silvl ether or the corresponding alcohol and an allylsilane (3) (b, Scheme 1). Catalysts that have been employed for such three-component Hosomi-Sakurai reactions using alkoxysilanes include Lewis acids such as trimethylsilyl iodide (TMSI),^[2] diphenyl-(Ph₂BOTf),^[3] trimethylsilyl triflate boryl triflate (TMSOTf),^[4,5] trimethylsilyl fluorosulfonate (TMSOFs),^[6] trimethylsilyl methanesulfonate (TMSOMs),^[7] iron chloride (FeCl₃),^[8] bismuth triflate [Bi(OTf)₃],^[9] and iron tosylate [Fe(OTs)₃].^[10] Some of these methods suffer from certain drawbacks including the involvement of compounds that are corrosive, difficult to handle, expensive or harmful, and the requirement of anhydrous conditions or low temperatures. Others represent rather one-pot procedures than true multicomponent reactions. A catalytic synthesis of homoallylic ethers starting from an aldehyde, an *alcohol*, and an allylsilane is underdeveloped.^[11,12]

We have previously developed Brønsted acid-catalyzed Hosomi–Sakurai reactions of dimethyl and dibenzyl acetals with allylsilanes.^[13] Here we report the first three-component variants in which aldehydes react with allylsilanes and either silyl ethers or their corresponding alcohols.^[14,15,16]

The key intermediate in allylations of acetals is presumably oxocarbenium ion **A**, which can be accessed *via* acid catalysis from the acetal (1) (path a) or *via* the reaction of an aldehyde (2) with a silyl ether (path b). Alternatively, we reasoned that it should also be possible to generate this intermediate more conveniently from an aldehyde (2) and an alcohol (path c). Nucleophilic attack of allyltrimethylsilane (3) to intermediate **A** would furnish the desired homoallylic ether (4) and Me₃SiX which could initiate further catalytic cycles (Scheme 2).

First, we investigated the reaction of benzaldehyde (5), benzyloxytrimethylsilane (BnOTMS) or benzyl

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Scheme 2. Possible Hosomi-Sakurai reaction pathways.

alcohol (BnOH), and allyltrimethylsilane (3). The benzyl substituent has been chosen due to its function as a conventional protecting group that can be cleaved under mild conditions. Studies towards the development of our previous Hosomi-Sakurai reaction revealed that 2,4-dinitrobenzenesulfonic acid (DNBA) is a powerful catalyst and acetonitrile a suitable solvent for the allylation of acetals. Therefore, we kept these parameters constant. Screening of the catalyst loading, the equivalents of the reagents, the concentration, as well as the temperature furnished our optimized conditions. Thus one equivalent of benzaldehyde (5) reacted with two equivalents each of the silvl ether and the allylsilane (3) in the presence of 3 mol% of DNBA to give the desired product (6) in 92% yield. As expected, BnOH turned out to be less reactive and the catalyst loading had to be increased to 5 mol%. In this case, three equivalents of allyltrimethylsilane in combination with two equivalents of the alcohol were required to afford homoallyl benzyl ether 6 in 72% yield. The large amount of allylsilane (3) might be rationalized by its partial consumption due to a possible in situ generation of BnOTMS from BnOH. Both variants of our multicomponent reactions were conducted at room temperature. Raising or lowering the temperature did not result in any improvement.

Using these newly developed conditions, we explored the scope and limitations of these two Hosomi–Sakurai reactions. Different carbonyl compounds were treated with BnOTMS and allyltrimethylsilane (3) in the presence of 3 mol% of DNBA to give homoallyl benzyl ethers (7) in moderate to high yields (Table 1). Aromatic aldehydes with electron-donating or electron-withdrawing substituents as well as heteroaromatic or α,β -unsaturated precursors are tolerated. Aliphatic aldehydes bearing a secondary,

Table 1. Three-component Hosomi–Sakurai reaction usingBnOTMS: variation of the aldehyde.



^[a] Yield of isolated product.

tertiary or quaternary carbon atom at the α -position can be used, too. Ketones were found to be inert. Apparently, our conditions are not suitable for the acetalization of ketones, as acetals derived from ketones have been successfully employed in our previous DNBA-catalyzed allylation. The combinations of aldehydes (2), BnOTMS and allyltrimethylsilane (3) are generally clean and complete within 3 to 12 h. Only in the cases of thiophene-3-carbaldehyde and cinnamaldehyde were the reactions stopped before complete consumption of the starting material (2) to avoid the formation of undesired by-products. In the reaction of crotonaldehyde several by-products were obtained and the corresponding benzyl ether (13) was isolated in a relatively low yield.

To compare the three-component reaction involving BnOTMS with the variant that employs the corresponding alcohol, representative aldehydes (2) have been investigated (Table 2). One aromatic, one heter-

Table 2. Three-component Hosomi–Sakurai reaction usingBnOH: variation of the aldehyde.



^[a] Yield of isolated product.

oaromatic, one α,β -unsaturated, as well as one aliphatic precursor were subjected to BnOH, allyltrimethylsilane (3), and 5 mol% of DNBA. While the yield of the aromatic homoallyl benzyl ether (6) is good, the products derived from thiophene-3-carbaldehyde, cinnamaldehyde, and pivalaldehyde were isolated in moderate yields. None of these reactions went to completion. Even after prolonged stirring for two days the starting aldehyde (2) could still be detected. Two reasons might be considered to explain the lower reactivity of this system. On the one hand, our conditions could be less suitable for the acetalization of aldehydes with BnOH than with the more reactive silyl ether. On the other hand, allyltrimethylsilane could be partially consumed due to a possible *in situ* generation of BnOTMS from BnOH. Consequently, less allylsilane might be available for the subsequent allylation.

Next, benzaldehyde (5) was treated with different silyl ethers or their alcohols and allyltrimethylsilane (18, $R^2 = H$) in the presence of catalytic amounts of DNBA to provide a high diversity of homoallylic ethers (19, $R^2 = H$) (Table 3). Both unsaturated alcohols/silvl ethers bearing a double bond or a triple bond and linear or branched saturated derivatives are tolerated. Aromatic alcohols/silyl ethers such as phenoxytrimethylsilane or phenol were found to be unreactive. The yields of the desired products derived allyloxytrimethylsilane from (AllOTMS), propargyloxytrimethylsilane (propargyl-OTMS), pentyloxytrimethylsilane (pentyl-OTMS) or isopropoxytrimethylsilane (i-PrOTMS) as well as from allyl alcohol (AllOH), 1-pentanol (pentyl-OH) or isopropyl alcohol (i-PrOH) are high. By way of contrast, homoallyl propargyl ether 21 was isolated in moderate vield when propargyl alcohol (propargyl-OH) was used. The combinations of benzaldehyde (5), silvl ethers or their alcohols, and allyltrimethylsilane (18, $R^2 = H$) are generally clean and complete within 2 to 5 h. Only the reaction of propargyl alcohol did not go to completion. Even after prolonged stirring for two days the starting aldehyde (5) was still detected.

Additionally, benzaldehyde (5) was subjected to BnOTMS or BnOH, methallyltrimethylsilane (18, $R^2 = Me$), and 3 or 5 mol% of DNBA (Table 3, entries 9 and 10). Replacing allyltrimethylsilane (18, $R^2 = H$) by a substituted allyl transfer reagent (18, $R^2 = Me$) significantly diminished the yield of the corresponding homoallylic ether (19, $R^2 = Me$).

Finally, we tested chiral sulfonic acids as catalysts for the reaction of benzaldehyde (5), BnOTMS, and allyltrimethylsilane (3). Commercially available camphorsulfonic acid (CSA, 25) did not give any conversion in dichloromethane, neither to the final product (6) nor to the intermediate acetal. In contrast, the more reactive binaphthalenyl disulfonic acid $(26)^{[17]}$ provided the desired homoallyl benzyl ether (6) in 80% GC yield (Scheme 3). However, no measurable enantioselectivity has been achieved so far.

In summary, we have developed Brønsted acid-catalyzed three-component Hosomi–Sakurai reactions. DNBA mediates the combination of aldehydes, alkoxysilanes, and allylsilanes to provide a wide range of homoallylic ethers in moderate to high yields. Furthermore, alcohols instead of their silyl ethers can be

	O R ¹ C Ph H R 5 R	отMS or + R ² ОН 18	$\begin{array}{c} O_2 N & NO_2 \\ \hline & (3 \text{ or } 5 \text{ mol}\%) \\ \hline & CH_3 CN, r.t. \end{array}$	OR ¹ R ² Ph 19	
Entry	R ¹ OTMS or R ¹ OH	\mathbb{R}^2	Product	Time [h]	Yield ^[a] [%]
1	AllOTMS	H	Ph 20	2	84
2	AllOH	H		3	80
3	Propargyl-OTMS	H	Ph 21	5	83
4	Propargyl-OH	H		24	55
5	Pentyl-OTMS	H	OPentyl	3	96
6	Pentyl-OH	H	Ph	3	93
7	<i>i</i> -PrOTMS	H	O- <i>i</i> -Pr	2	93
8	<i>i</i> -PrOH	H	Ph	3	90
9	BnOTMS	Me	OBn Me	24	66
10	BnOH	Me	Ph	24	52

 Table 3. Three-component Hosomi-Sakurai reactions: variation of the silyl ether, the alcohol, and the allylsilane.

^[a] Yield of isolated product.



Scheme 3. Screening of chiral sulfonic acids.

employed as well. Significant advantages of our processes include: a) the use of commercially available starting materials, b) the broad scope, c) a high diversity of the products, and d) the simplicity and practicability.

Most notably, DNBA is a powerful and useful catalyst: a) it is very active resulting in low catalyst loadings, b) it is commercially available and can be used without any further purification, c) it is inexpensive, nontoxic, and easy to handle, and d) it does not require anhydrous conditions and can be stored under air over a long period. Hence, it has certain advantages over many Lewis acids.

Although the use of chiral sulfonic acids has so far not led to any enantioselectivities yet, we anticipate solutions to this problem to arise in the near future.

Experimental Section

General Procedure for the Three-Component Hosomi–Sakurai Reaction of Aldehydes, Alkoxysilanes, and Allylsilanes

Aldehyde **2** (1 mmol, 1.0 equiv.), an alkoxysilane (2 mmol, 2.0 equiv.), and allylsilane **18** (2 mmol, 2.0 equiv.) were added to a solution of DNBA (8.5 mg, 0.03 mmol, 3 mol%) in anhydrous CH₃CN (1.5 mL) and stirred at room temperature for the indicated time. The mixture was poured into brine (20 mL) and extracted with Et₂O (3×50 mL). The combined organic layers were washed with aqueous NaHCO₃ (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated. Homoallylic ether **19** was isolated by flash chromatography (silica, pentane/CH₂Cl₂ or pentane/Et₂O).

General Procedure for the Three-Component Hosomi–Sakurai Reaction of Aldehydes, Alcohols, and Allylsilanes

Aldehyde **2** (1 mmol, 1.0 equiv.), an alcohol (2 mmol, 2.0 equiv.), and allylsilane **18** (3 mmol, 3.0 equiv.) were added to a solution of DNBA (14.2 mg, 0.05 mmol, 5 mol%) in anhydrous CH₃CN (4.5 mL) and stirred at room temperature for the indicated time. The mixture was poured into brine (20 mL) and extracted with Et₂O (3×50 mL). The combined organic layers were washed with aqueous NaHCO₃ (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated. Homoallylic ether **19** was isolated by flash chromatography (silica, pentane/CH₂Cl₂ or pentane/Et₂O).

Supporting Information

The Supporting Information comprises a general procedure for the screening of chiral sulfonic acids as well as analytical data for the characterization of new compounds (NMR, HR-MS).

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