Recent Advances in the Direct Nucleophilic Substitution of Allylic Alcohols through $S_N1$-Type Reactions

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Abstract: Direct nucleophilic substitution reactions of allylic alcohols are environmentally friendly, since they generate only water as a byproduct, allowing access to new allylic compounds. This reaction has, thus, attracted the interest of the chemical community and several strategies have been developed for its successful accomplishment. This review gathers the latest advances in this methodology involving $S_N1$-type reactions.

1 Introduction

The need to save resources and concerns about our environment have led to the development of new strategies in organic synthesis that are able to fulfill these requirements.1 Thus, new environmentally friendly processes have been established that minimize waste production by applying the atom-economy concept2 and avoiding the use of toxic or expensive reagents and/or catalysts.

The allylic substitution reaction is a widespread methodology that is successfully employed in organic synthesis to obtain new allylic compounds.3 Traditionally, this process employs alcohol derivatives, such as allylic carbonates, acetates, phosphates, and halides as substrates, and this generates a stoichiometric amount of waste in their preparation and on their reaction with the corresponding nucleophile. Therefore, a more attractive strategy from both a practical and environmentally point of view would be the direct use of allylic alcohols in this transformation, since they are readily available compounds and water would be the only byproduct formed (Scheme 1).1

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Scheme 1 Direct and indirect routes for allylic substitution reactions
2 S$_{N}$1-Type Direct Nucleophilic Substitution Reactions of Allylic Alcohols

The advantages of free alcohols in allylic substitution reactions have the attention of organic chemists, and numerous procedures have been devised to accomplish this purpose. However, free allylic alcohols have two main drawbacks: the poor ability of the hydroxyl function as a leaving group and the formation of a stoichiometric amount of water; this requires the use of a water-tolerant catalyst able to activate the hydroxy group. Thus, three main strategies, based on the catalysts employed, have been developed to overcome these problems (Scheme 2):

The use of transition-metal-based catalysts (such as Pd, Ir, Pt, Rh etc.) implying a π-allyl intermediate in a Tsuji–Trost-type reaction.4

The employment of Brønsted or oxophilic Lewis acids forming the corresponding carbocationic intermediate in an SN1-type reaction.5

The use of soft π-Lewis acids, such as Au(I) or Hg(II), able to activate the double bond, and hence facilitating the nucleophilic attack in an SN2′-type reaction.6

This review discusses the most relevant recent work published since 2011 that uses catalysts or promoters, which implies the formation of a carbocationic intermediate in an SN1-type reaction, for direct allylic substitution reactions using free alcohols.5

2.1 Lewis Acids as Catalysts

The use of oxophilic Lewis acids as catalysts grows rapidly, despite the great progress already achieved.5 Generally, the Lewis acids employed tend to be readily available.7 As depicted in Scheme 3, the mode of activation of these catalysts consists of the interaction of the Lewis acid (LA) with the hydroxyl group, forming a hydroxo–anionic complex and the allylic carbocation intermediate. After attack of the nucleophile and proton release, the Lewis acidity is re-established by the loss of a molecule of water.

Our group has reported the use of silver(I) triflate for the direct amination of allylic alcohols; silver salts are readily available Lewis acids that had not previously been used in direct intermolecular allylic substitution reactions using allylic alcohols.8 The use of silver(I) triflate in low catalyst loadings (2–5 mol%) allowed the successful amination of various allylic alcohols with sulfonamides, carbamates, and anilines [Scheme 4, (a)].

The Che group also used silver(I) triflate for the allylation of electron-rich arenes and heteroarenes in a Friedel–Crafts-type reaction that achieved good to excellent results [Scheme 4, (b)].9 Che and co-workers also described the use of Ag$_3$PW$_{12}$O$_{40}$ as a heterogeneous catalyst for this transformation that gives comparable results; Ag$_3$PW$_{12}$O$_{40}$ was recyclable by simply filtration for up to five cycles.9 Rueping and co-workers described the use of silver(I) triflate for the direct azidation of allylic alcohols [Scheme 4, (c)].10 In all cases the regioselectivity of the process was governed by the stability of the carbocation intermediate.

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Another late transition metal that had not previously been frequently employed in this type of transformation is copper.5 The Wang and Zhang group reported the formation of C–C bonds between terminal alkynes and allylic alcohols catalyzed by Cu(OTf)$_2$, with low catalyst loadings (0.5 mol%) and using 1,2-dibromoethane as the solvent. Remarkably, other Lewis and Bronsted acids commonly employed in direct substitution reactions of alcohols failed or, at best, gave poor results for this particular trans-
formation. This methodology was also applied to benzylic alcohols (Scheme 5).\textsuperscript{11}

\begin{equation}
\text{Ar} \quad \text{OH} \quad \text{Ar} \\
\text{Cu(OTf)}_2 (0.5 \text{ mol\%}) \quad \text{BrCH}_2\text{CH}_2\text{Br} \quad 120 \degree \text{C} \\
\text{71–84\%}
\end{equation}

Scheme 5  Alkynylation of allylic alcohols catalyzed by Cu(OTf)\textsubscript{2}

As discussed, Au(I) is considered as a π-phlic Lewis acid, and, therefore, a carbocationic intermediate is rarely involved when their complexes are used for this reaction.\textsuperscript{6,12} However, Au(III) is not the same, as in this higher oxidation state the gold species are considered oxophilic and can activate the hydroxyl group generating a carbocation.\textsuperscript{5} Thus, the Ohshima and Mashima group took advantage of this well-known fact,\textsuperscript{6} and they reported the use of NaAuCl\textsubscript{4}·2H\textsubscript{2}O (1 mol\%) for the direct allylic amination reaction of different linear allylic alcohols using highly functionalized nitrogen nucleophiles (containing other functional groups such as protected alcohols, carbonyl groups, acetals etc.) in refluxing dichloromethane.\textsuperscript{13} This group also described the use of aluminum salts, more precisely Al(OTf)\textsubscript{3}, which were unexplored as catalysts for this type of transformation.\textsuperscript{14} In this case only 1 mol\% of catalyst loading in nitromethane as solvent was sufficient to achieve high yields within minutes for most examples described. In both cases, the observed racemization of optically enriched substrates during the substitution process supports an S\textsubscript{n}1-type mechanism. In addition, in the case of Al(OTf)\textsubscript{3}, the authors also performed the direct amination under microwave irradiation and this shortened the reaction times, especially in the most challenging examples, and maintained the excellent results.\textsuperscript{14}

The same racemization in the aminated product when starting from an enanitioenriched allylic alcohol was observed by Yamamoto and co-workers for the intermolecular amination of alcohols using sulfamates as nucleophiles and Hg(OTf)\textsubscript{2} as catalyst, which, as in the previous gold case, is commonly classified as a soft π-Lewis acid. This fact, together with double bond isomerizations, points towards an S\textsubscript{n}1-type mechanism. Thus, high yields were obtained at room temperature with only 2 mol\% catalyst loading. The reaction shows high functional group tolerance, although in some cases higher temperatures were needed. In addition, a supported version of this catalyst was also successfully employed and reused for up to five cycles by simply filtration without apparent metal leaching, for example, in the reaction between cyclohex-2-enol (1) and methyl sulfamate (2) (Scheme 6).\textsuperscript{15}

\begin{equation}
\begin{aligned}
\text{Ar} \quad \text{OH} & + \quad \text{Ph} \\
\text{Cu(OTf)}_2 (0.5 \text{ mol\%}) & \\
\text{BrCH}_2\text{CH}_2\text{Br} & \quad 120 \degree \text{C} \\
\text{71–84\%}
\end{aligned}
\end{equation}

Scheme 6  A supported mercury(II) salt as a recyclable catalyst

Zinc(II)-based salts efficiently catalyze the direct allylic substitution of alcohols employing 1,3-dicarbonyl compounds as nucleophiles under microwave irradiation.\textsuperscript{5,16} An additional attractive application from an environmental point of view has been developed based on the use of ZnBr\textsubscript{2} acting as a catalyst for the solvent-free allylic substitution reaction of alcohols, using indoles and nitrogen compounds (mainly sulfonamides and electron-poor amines) as nucleophiles under high-speed vibration milling conditions. Other common Lewis acids employed in this reaction, such as FeCl\textsubscript{3}, AlCl\textsubscript{3}, and CuCl\textsubscript{2}, afforded the corresponding products in lower yields under the same conditions. Unfortunately, a relatively high catalyst loading (20 mol\%) was necessary to achieve high yields.\textsuperscript{17}

In addition, a further two processes use zinc salts in a C–C bond-forming reaction. The first uses 15 mol\% Zn(OTf)\textsubscript{2} as the catalyst and TMSCN (4) as the cyanide source for the direct cyanation of benzylic and allylic alcohols, such as (E)-1,3-diphenylprop-2-en-1-ol (3), giving the corresponding nitriles in good yields (Scheme 7).\textsuperscript{18}

\begin{equation}
\begin{aligned}
\text{Ph} \quad \text{OH} & + \quad \text{TMSCN} \\
\text{Zn(OTf)}_2 (15 \text{ mol\%}) & \\
\text{MeNO}_2 & \quad 100 \degree \text{C} \\
\text{77\%}
\end{aligned}
\end{equation}

Scheme 7  Cyanation of allylic alcohols catalyzed by zinc triflate

The second process, from the Ma group, uses allenes as nucleophiles in the reaction with in situ formed carbocations derived from allylic alcohols. In this case zinc halides, although used in stoichiometric amounts, were the promoters. Depending on the allene structure and the zinc halide employed, different products were isolated (Scheme 8). Thus, when the R group was alkyl or aryl and ZnCl\textsubscript{2} was employed, the corresponding indene derivatives were obtained as a consequence of nucleophilic attack of the allene on the transient carbocation followed by a Friedel–Crafts-type reaction. However, for monosubstituted allenes (R = H), the corresponding halopenta-1,4-dienes were obtained regardless of the zinc salt employed.\textsuperscript{19}
Scheme 8 Allenes as nucleophiles in zinc(II)-mediated reactions with allylic alcohols

Bismuth(III) triflate is an excellent catalyst for the direct allylic substitution of free alcohols.\(^{5,20}\) However, a new protocol by the Laali group uses ionic liquids as environmentally friendly and reusable reaction media in combination with 10 mol% of Bi(OTf)\(_3\) as the catalyst. Under these conditions silyl-based nucleophiles were successfully introduced in short reaction times affording the corresponding products in high yields (Scheme 9). The ionic liquid [BMIN][BF\(_4\)] was recovered for up to six cycles without affecting the chemical yield.\(^{21a}\) A similar strategy, but using Bi(NO\(_3\))\(_3\)·5 H\(_2\)O as the catalyst, was followed by the same group when using 1,3-dicarbonyl compounds as nucleophiles.\(^{21b}\)

Scheme 9 Bismuth(III)-catalyzed allylic substitution of alcohols in ionic liquids

Other metal species that act as Lewis acids which are able to catalyze the direct allylic substitution of alcohols that had not previously been explored are SbCl\(_3\) and Re\(_2\)O\(_7\). Nayak et al. used SbCl\(_3\) as a catalyst for the allylation (and alkylation using benzylic alcohols) of electron-rich arenes and heteroarenes with (E)-1,3-diphenylprop-2-en-1-ol (3) as the substrate in a microwave-accelerated reaction that achieved good yields in short reaction times, although a relatively large amount of catalyst (15 mol%) was needed [Scheme 10, (a)].\(^{22}\) In contrast, Re\(_2\)O\(_7\) showed excellent activity as a catalyst for the amination of allylic alcohols with different nitrogen-containing nucleophiles; only 1.5 mol% of Re\(_2\)O\(_7\) was required at room temperature to reach high yields [Scheme 10, (b)].\(^{23}\)

Scheme 10 Antimony(III)- and rhenium(VII)-catalyzed allylic substitution

The use of tin as a catalyst for this transformation has received scant study. However, the Roy group has reported the use of heterobimetals Sn–Pd and Sn–Ir complexes, PdCl(COD)–SnCl\(_3\) and [Ir(μ-Cl)(COD)Cl(SnCl\(_3\))]\(_2\), respectively, for direct nucleophilic substitution through dual activation of allylic alcohols.\(^{24}\) Under these conditions a wide variety of nucleophiles, such carbon nucleophiles, e.g. 1,3-dicarbonyl compounds and arenes, organosilanes, nitrogen-based nucleophiles, alcohols, and thiols, have been successfully introduced even using less reactive allylic alcohols such as cinnamyl alcohol. The dual activation, which was corroborated by \(^1\)H and \(^{13}\)C NMR, of the hydroxy group by the Lewis acid and the double bond by the transition metal (Pd or Ir), respectively, is thought to be responsible for the good yields obtained (Figure 1).\(^{24}\)

Figure 1 Proposed activation mode of heterobimetals Sn–Pd and Sn–Ir complexes

The alkaline-earth metals have attracted much less attention as Lewis acids that are able to activate the hydroxy group and, hence, promote this transformation. The Niggemann group has studied the use of calcium salts as catalysts for the direct substitution of alcohols in an \(S_\text{N}1\)-type reaction. Concretely, they have successfully utilized calcium triflimide in combination with an ammonium salt for the nucleophilic substitution reactions of various allylic alcohols. Thus, depending on the nucleophile employed the direct amination, Friedel–Crafts-type arylation, and alkylation/alkenylation reaction were achieved (Scheme 11).\(^{25}\)
Iodine efficiently catalyzes the direct allylic substitution reaction of alcohols under mild conditions giving satisfactory results with different nucleophiles.\textsuperscript{5} The Liu group took advantage of this fact and applied this methodology to the allylation of a wide variety of nucleophiles, such as arenes, nitrogen nucleophiles, and 1,3-dicarbonyl compounds, achieving excellent results.\textsuperscript{26}

The Ji group used the combination of Fe/I$_2$/NaI in stoichiometric amounts for the synthesis of alkenyl iodides in good yields and diastereoselectivities through the reaction of alkynes with allylic and benzylic alcohols (a representative example is shown in Scheme 12).\textsuperscript{27} Although the exact mechanism remains unclear, it is proposed that a carbocation derived from the corresponding alcohol is formed by reaction either with iodine or iron.

Iron(III) chloride has already shown its effectiveness as a catalyst for this synthetic transformation in its inter- and intramolecular versions.\textsuperscript{5,28} However, our research group used FeCl$_3$·6 H$_2$O, which, in contrast to anhydrous FeCl$_3$, had been used previously, is more economic and can be used in an open-air flask using technical grade solvents. Our work focused on direct allylic amination reactions with free alcohols using FeCl$_3$·6 H$_2$O or TfOH as a catalyst for this synthetic transformation in its inter- and intramolecular versions.\textsuperscript{5,28} However, our research group took advantage of this fact and applied this methodology to the allylation of a wide variety of nucleophiles, such as silyl-based, aromatics, and malonates were also successfully allylated employing this methodology.\textsuperscript{26}

We have also developed a greener strategy using this methodology; the catalyst FeCl$_3$·6 H$_2$O is used with water as the solvent.\textsuperscript{30} This protocol is the first example of the use of a Lewis acid in direct nucleophilic substitution reactions with free allylic alcohols in pure water in an S$_\text{N}$1-type reaction. As expected, harsher conditions were necessary to reach satisfactory results; using 10 mol% FeCl$_3$·6 H$_2$O at a temperature of 90 °C gave similar or slightly inferior results to those obtained in organic solvents (Scheme 14). However, it is remarkable that some carbon nucleophiles, such as TMSCN (4), which failed completely when the reaction was carried out in organic solvents, produced the desired product in water, although in a modest 45% yield. The need for the use of more forcing conditions can be easily understood from a solubility point of view, but also can be ascribed to the formation of less Lewis acidic species [Fe(H$_2$O)$_{6-n}$(OH)$_n$]$_{3-n}$Cl$_3$.\textsuperscript{30}
The Wang and Sun group used FeCl₃·6 H₂O in the synthesis of dihydroquinolines through an intramolecular direct amination (Scheme 15); high yields were obtained under mild reaction conditions and using low catalyst loadings. In addition, the obtained dihydroquinolines were readily transformed in almost quantitatively yields into the corresponding quinolines following basic treatment.31

Finally, the Kaper group used ZrO₂, which to the best of our knowledge has not previously been used for this type of transformation, acting as a supported Lewis acid in a SiO₂–ZrO₂ mixed oxide structure, in the Friedel–Crafts alkylation of anisole with cinnamyl alcohol (Scheme 16, (a)). The best results were achieved when molar ratio of SiO₂–ZrO₂ was 95:5 (named SiZr5). Of particular interest is the result obtained when (E)-1,3-diphenylprop-2-en-1-ol (3) was reacted at 110 °C with benzyl alcohol as the solvent. The desired result was an intramolecular Friedel–Crafts reaction and subsequent transfer hydrogenation (MPV-type) of the double bond to obtain the product 10, but instead the major product was the cyclopropane derivative 11, the result of the hydrogenation of cyclopropene 12 [Scheme 16, (b)].32

2.2. Brønsted Acids as Catalysts

The use of Brønsted acids (BA) as catalysts for the direct nucleophilic substitution of allylic alcohols has experienced significant growth as, despite their simplicity and availability, they were previously unexploited and they

had not been considered as potential catalysts for this transformation, with the exception of some sulfonic acids.5 The mode of action is simple, as depicted in Scheme 17. Thus, the protonation of the hydroxyl group by the Brønsted acid affords, after dehydration, the corresponding stabilized allyl carbocation that reacts with the nucleophile regenerating the Brønsted acid after proton release.

Sulfonic acids have been the most successful Brønsted acids employed so far as catalysts for this type of transformation. This success prompted our research group, among others, to explore TFOH as a potential catalyst. Thus, we chose this strong acid for the direct amination of allylic alcohols in a comparative study with FeCl₃·6 H₂O as both are readily available catalysts.29 In this case, we observed

\[
\text{Scheme 15} \quad \text{Synthesis of dihydroquinolines catalyzed by FeCl₃·6 H₂O by an intramolecular amination of allylic alcohols}
\]
that generally TfOH performed slightly better than the Fe(III) salt and as little as 1 mol% of catalyst was sufficient to effectively promote the direct amination of a wide variety of allylic alcohols using dioxane as solvent at 25 °C in most cases. Remarkably, good yields (although higher temperatures were required) were achieved even when more challenging substrates, such as linear primary allylic alcohols cinnamyl alcohol (9) and (E)-but-2-en-1-ol (13) were used; utilizing FeCl₃·6 H₂O with the same substrate with high temperatures and catalyst loadings gave the corresponding products in low yields (Scheme 18). However, it is important to note that the reaction with TfOH failed completely using water as the solvent, this is in contrast to FeCl₃·6 H₂O.

**Scheme 18** Direct amination of linear primary allylic alcohols catalyzed by TfOH

This direct amination reaction has been also described using sulfonic acid functionalized ionic liquids as catalysts (Figure 2). The reaction proceeds well in terms of yield for different sulfonamides, amides, and anilines, when 10 mol% of the ionic liquids was used in dioxane at 80 °C and with (E)-1,3-diphenylprop-2-en-1-ol (3) as the substrate of choice. The catalyst can be recovered by simply aqueous extraction from the reaction crude and reused up to six times without significant loss of activity.33

Jin et al. described an interesting transformation also catalyzed by TfOH and leading to Cₛᵖ³–Cₛᵖ² bond formation. The reaction of allylic (and benzylic) alcohols with styrene and other alkenes (Scheme 19), gave particularly high yields for alcohol 3.34

**Scheme 19** Cₛᵖ³–Cₛᵖ² Bond formation catalyzed by TfOH

Although the effectiveness of 4-toluenesulfonic acid (PTSA) as the catalyst in this type of transformation has been clearly demonstrated, especially by the Sanz group,35 remarkable work has now been published on the use of PTSA as a catalyst in Sₙ1-type reactions (Scheme 20). Reddy et al. described a highly stereoselective C₅-alkylation of oxoindoles with different alcohols. Interestingly, the alkylation occurs at C₅ and not at C₃ (α-alkylation) as happens when Lewis acids or basic media are employed [Scheme 20, (a)].36 In contrast, the α-alkylation of carbonyl compounds, such as aldehydes, was obtained using PTSA under mild reaction conditions with excellent results especially for (E)-1,3-diphenylprop-2-en-1-ol (3) [Scheme 20, (b)].37,38

The α-alkylation of various aldehydes using alcohol 3 has been also reported using PTSA (20 mol%) with acetonitrile as the solvent in combination with a polysiloxane (10 mol%) bearing a secondary amine in the structure in a dual activation strategy. Thus, whereas PTSA activates the allylic alcohol forming the corresponding carbocation, the amine forms the corresponding enamine, therefore activating the aldehyde. The yields obtained were moderate.
Liu and co-workers reported that other strong acids such as sulfuric and tetrafluoroboric acid effectively accomplish the direct substitution of alcohols with 1,3-dicarbonyl compounds under conventional or microwave-assisted heating. Only a few examples of allylic substitution were given using alcohol 3 as the substrate, however, the corresponding products were obtained in high yields. In both cases employed 5 mol% of catalyst loading with nitromethane as the solvent.

The Aoyama group employed NaHSO₄ supported on silica gel (2.1 mmol NaHSO₄/g silica gel) in a heterogeneous allylation of dicarbonyl and arenes compounds with free alcohols; good yields were obtained when 3 was the allylic alcohol employed. The use of less activated alcohols result in lower yields and, for example, the reaction of cinnamyl alcohol failed completely under these conditions. The reaction was generally performed at 80 °C with 1,2-dichloroethane as the solvent of choice. However, it is remarkable that the catalyst can be recycled up to nine times if it is separated from the reaction media and dried under vacuum prior to reuse.

The McCubbin group described the use of pentafluorophenylboronic acid in intermolecular, Friedel–Crafts-type, allylic substitution reactions of alcohols using different arenes and heteroarenes. From this precedent, the Hall group reported an intramolecular carbo- and heterocyclization reaction employing this catalyst (Scheme 21) to obtain a wide variety of heterocycles. The reaction is simple, works under mild conditions (r.t.) and high yields (63–98%) are obtained within short reaction periods (normally less than 1 h) even with low catalyst loadings (<3 mol%) using dichloromethane as the solvent for a wide variety of linear allylic alcohols.

2.3 Other Promoters

In the search for a simple and metal-free strategy and lower-acidic conditions for the direct nucleophilic substitution of allylic alcohols and, due to their unique properties, such as high hydrogen bond donor ability, high polarity, and ionizing power along with low nucleophilicity, we envisaged fluorinated alcohols as a reaction medium that would be able to mediate this transformation. Particularly, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propan-2-ol (HFIP) were used as solvents and promoters of allylic substitution reactions of various alcohols using as nucleophiles with good results; these reactions general-

![Figure 3 Recyclable polysiloxane for the α-alkylation of aldehydes](image)

**Scheme 21** Intramolecular carbo- and heterocyclization of allylic alcohols catalyzed by pentafluorophenylboronic acid

Acids cannot be discounted, for the cyanation of various allylic alcohols. It is claimed that the presence of these metals enhances the Brønsted acidity of montmorillonites, since their absence, or the presence of others metals, produced poor results at best. The reaction proceeds under mild conditions (r.t.) and high yields (63–98%) are obtained within short reaction periods (normally less than 1 h) even with low catalyst loadings (<3 mol%) using dichloromethane as the solvent for a wide variety of linear allylic alcohols.

Finally, montmorillonites are excellent solid Brønsted acids that are able to accomplish direct nucleophilic substitution of free alcohols. Onaka and co-workers have reported the use of highly active Sn- and Ti-based montmorillonites, acting as heterogeneous Brønsted acids (although a secondary role of the metals acting as Lewis acids cannot be discounted), for the cyanation of various allylic alcohols.

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Another field that is still undeveloped is the use of allylic alcohols in enantioselective transformations through a \( S_N_1 \)-type reaction.\(^5\) In this regard, some advances, mainly focused on organocatalytic transformations, have been reported. However, the scope of allylic alcohols is still limited and only those that generate a highly stable carboxatic intermediate have been employed so far. Therefore, new methodologies that would allow a broader substrate scope are required.

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(12) Our group, among others, reported the use of cationic gold(I) complexes for the direct amination reaction onto free allylic alcohols (see refs. 6 and 8).

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