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Brønsted Acid-Catalyzed Nucleophilic Substitution of Alcohols

Roberto Sanz,[a,*] Alberto Martínez,[a] Delia Miguel,[a] Julia M. Álvarez-Gutiérrez,[a] and Félix Rodríguez[b]

[a] Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos, s/n, 09001-Burgos, Spain
Fax: (+34)-947-258-831; e-mail: rsd@ubu.es
[b] Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, C/Julián Clavería, 8, 33006-Oviedo, Spain

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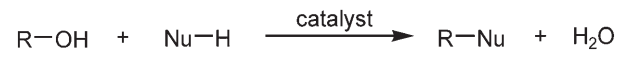
Abstract: Simple Brønsted acids such as *p*-toluenesulfonic acid monohydrate (PTS) or polymer-bound *p*-toluenesulfonic acid efficiently catalyze the direct nucleophilic substitution of the hydroxy group of allylic and benzylic alcohols with a large variety of carbon- and heteroatom-centered nucleophiles. Reaction conditions are mild, the process is conducted under an atmosphere of air without the need for dried solvents, and water is the only side product of the reaction.

Keywords: alcohols; C–C coupling; nucleophilic substitution; supported catalysts; synthetic methods

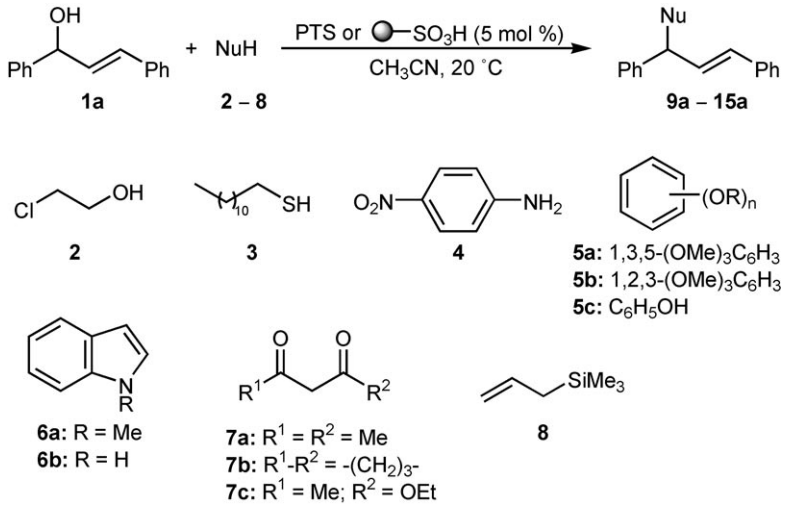
The construction of C–C bonds is a fundamental reaction in organic synthesis and coupling reactions between reactive nucleophiles (NuH) and halides (RX) or related species are one of the most used strategies. In this context, direct substitution of the hydroxy group in alcohols by nucleophiles could be considered as an ideal process because of the wide availability of the starting materials and the generation of H_2O as the only side product. However, the main limitation of this strategy is that an excess of sulfuric acid, polyphosphoric acid,[1] or a stoichiometric amount of a Lewis acid[2] is required, and so the range of possible nucleophiles is limited. Therefore, the development of catalytic versions of this reaction remains as a major objective of the modern organic chemistry (Scheme 1). Recent advances in this field are based on the use of transition metal complexes as catalysts. Remarkable are the Ru-,[3] Re-,[4] and Au-catalyzed[5] propargylation of nucleophiles with propargylic alcohols, the Tsuji–Trost reaction of allylic alcohols with active methylene compounds,[6] the reaction of secondary benzylic alcohols with different nucleophiles catalyzed by La, Sc, or Hf salts,[7] and the Fe-, or Au-catalyzed arylation of benzylic alcohols.[8] In addition, $InCl_3$ has emerged as a powerful catalyst to perform direct nucleophilic substitution of allylic and benzylic alcohols.[9]



Scheme 1. Ideal reaction for nucleophilic substitution of alcohols.

Although the catalytic activation of alcohols is thought to be difficult due to the poor leaving ability of the OH group, we have recently found that simple Brønsted acids like *p*-toluenesulfonic acid monohydrate (PTS) catalyze the direct nucleophilic substitution of propargylic alcohols.[10] Herein we report a strategy involving simple Brønsted acid-catalyzed activation of allylic and benzylic alcohols as a method for the direct formation of new C–C and C–heteroatom bonds from carbon (active methylene compounds, aromatic and heteroaromatic compounds), nitrogen, sulfur, and oxygen nucleophiles and alcohols. Surprisingly, the Brønsted acid-catalyzed direct substitution of allylic alcohols has not been reported in the literature and so no systematic study has so far been performed. Moreover, in some recent papers this reaction has been reported not to proceed at all.[9b]

Despite all these negative forewarnings, we decided to investigate the reaction of allylic alcohol **1a** as a model substrate with selected nucleophiles **2–8** under PTS-catalyzed conditions (Scheme 2). To our surprise, all nucleophiles coupled very well with **1a** when the reaction was performed with 5 mol% of PTS as catalyst in CH_3CN at room temperature, affording the substitution products **9–15** in high yields (Scheme 2 and Table 1). As shown, not only heteroatom-centered (**2–4**) (Table 1, entries 1–3) but also carbon-centered (**5–8**) nucleophiles are appropriate partners for



Scheme 2. PTS-catalyzed substitution reactions of **1a** with selected nucleophiles **2**–**8**.

Table 1. Nucleophilic substitution reactions of alcohol **1a**.

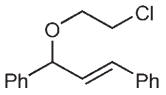
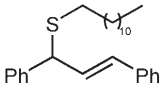
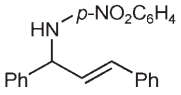
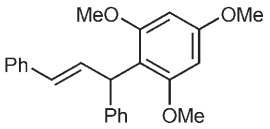
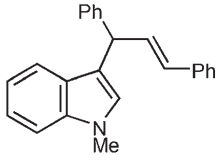
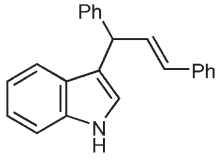
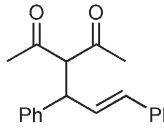
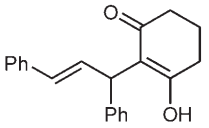
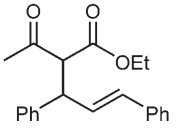
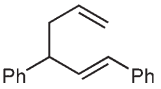
Entry	NuH	Product		Yield [%][a]
1	**2**		**9a**	83
2	**3**		**10a**	81
3	**4**		**11a**	86
4	**5a**		**12aa**	75
5	**6a**		**13aa**	84
6	**6b**		**13ab**	74
7	**7a**		**14aa**	84 (86)[b]
8	**7b**		**14ab**	80

Table 1. (Continued)

Entry	NuH	Product		Yield [%][a]
9	**7c**		**14ac**	72[c]
10	**8**		**15a**	90

[a] Isolated yield based on the starting alcohol **1a**.
[b] Isolated yield (7.5 g) from a 30 mmol scale reaction.
[c] Mixture of diastereoisomers (*ca.* 1:1).

this reaction. Thus, active methylene compounds **7** (Table 1, entries 7–9) and allylsilane **8** (Table 1, entry 10) have been successfully used. Moreover, interesting Friedel–Crafts allylations of arenes **5** (Table 1, entry 4) or indoles **6** (Table 1, entries 5 and 6) occur with high selectivity and yield. Due to the high interest in the regioselective alkylation of indoles,[11] it is remarkable that this methodology gives rise selectively to 3-alkylated products without formation of the corresponding *N*- or 2-substituted indole derivatives. It is also important to remark that these reactions can also be performed using catalytic amounts (5 mol%) of commercially available polymer-bound *p*-toluenesulfonic acid. Similar or even slightly higher yields are obtained under these conditions and, moreover, the isolation of the product by simple filtration of the solid supported acid is much easier.[12] Also, a large-scale synthesis of **14aa** was successful (7.5 grams, 86% yield after filtration of the solid acid and simple crystallization).

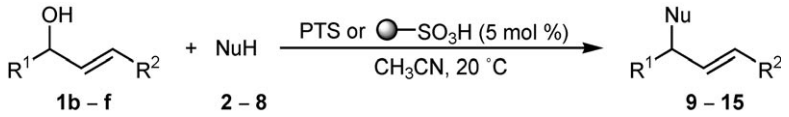
In order to test the scope of the reaction with respect to the starting allylic alcohol, we performed a set of experiments using differently substituted alcohols **1b–f** (Table 2). The reactions of the alcohols **1b** and **1c** afforded in some cases regioisomeric mixtures (Table 2, entries 2,4). Interestingly, alcohol **1c** gave rise to the same products, with similar yields and regioselectivity, as those obtained with **1b** (Table 2, entries 1, 2, and 4). This fact supports the same allylic cation as intermediate for both allylic alcohols. The same situation is observed with cinnamyl alcohol **1e** and α-vinylbenzyl alcohol **1f** (Table 2, entries 6 and 7). Again, very similar results were achieved by the use of the polymer-supported PTS as catalyst with the advantage of the very simple removal of the catalyst and the possibility of reusing it.

We then turned our attention to the catalytic direct nucleophilic substitutions of simple benzylic alcohols **1g–j** (Table 3).[13] Several solvents and conditions were tried and we have found that optimum results were obtained by using 10 mol% of PTS or polymer-supported PTS in CH_2Cl_2 at reflux.[14] As shown in Table 3, the reaction is general for different benzylic alcohols **1g–j** and the selected hetereoatom- and carbon-centered nucleophiles.

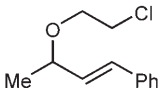
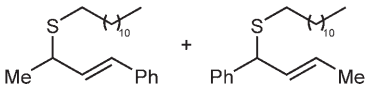
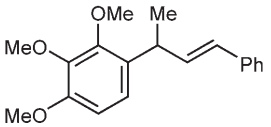
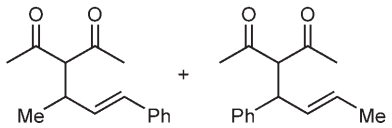
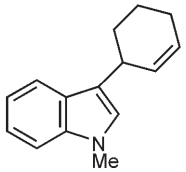
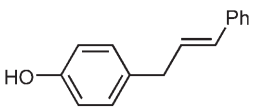
Regarding the mechanism, the reactions probably proceed through the formation of a stabilized carbonium intermediate and so two pathways are plausible and probably competitive for the substitution reactions: a direct substitution of the acid-activated alcohol and/or dimerization of the starting alcohol and subsequent substitution.[15] The main decomposition pathway of secondary benzylic alcohols is *via* the generation of olefins as shown by the side products obtained in the reactions of **1g**[16] and **1j** (Table 3, entries 3 and 10).

In summary, we have developed a PTS-catalyzed method for the direct nucleophilic substitution of hydroxy groups by a range of heteroatom- and carbon-centered nucleophiles under mild conditions. The process is conducted in an open flask, using analytical grade solvents and water is the only side product of

Table 2. PTS-catalyzed substitution reactions of allylic alcohols **1b–f**.

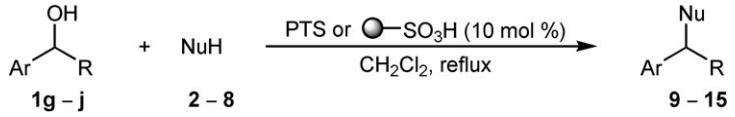


1b – f **2 – 8** **9 – 15**

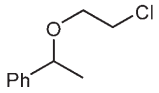
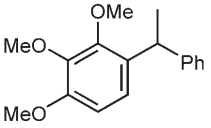
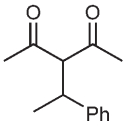
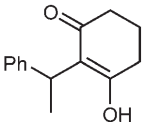
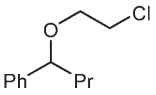
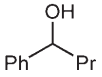
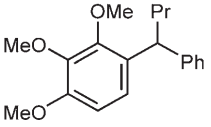
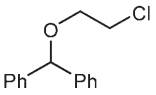
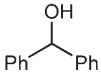
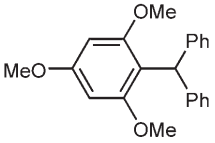
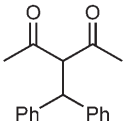
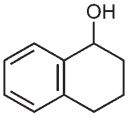
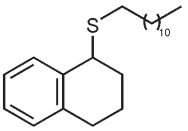
Entry	Alcohol	R^1	R^2	NuH	Product		Yield [%][a]
1	**1b**	Me	Ph	**2**		**9b**	77[b]
2	**1b**	Me	Ph	**3**		**10b** (70:30)	65[b]
3	**1b**	Me	Ph	**5b**		**12bb**	72
4	**1c**	Ph	Me	**7a**[c]		**14ba** (75:25)	79[b]
5	**1d**	-$(CH_2)_3$-		**6a**[c]		**13da**	55
6	**1e**	H	Ph	**5c**[c]		**12ec**	58[d]
7	**1f**	Ph	H	**5c**[c]			64[d]

[a] Isolated yield based on starting alcohol **1**.
[b] Independently on using **1b** or **1c** as starting material, similar results were obtained.
[c] Run at reflux.
[d] Minor amounts of the corresponding *ortho*-substituted product are observed.

Table 3. PTS-catalyzed substitution reactions of benzylic alcohols **1g–j**.



1g – j 2 – 8 9 – 15

Entry	Alcohol		NuH	Product		Yield [%][a]
1			**2**		**9g**	81
2			**5b**		**12gb**	76
3		**1g**	**7a**		**14ga**	70[b]
4			**7b**		**14gb**	64
5			**2**		**9h**	73
6		**1h**	**5b**		**12hb**	58
7			**2**		**9i**	84
8		**1i**[c]	**5a**		**12ia**	74
9			**7a**		**14ia**	85
10		**1j**	**3**		**10j**	65[d]

[a] Isolated yield based on the starting alcohol **1**.
[b] 15% of 1,3-diphenylbut-1-ene was also isolated.[16]
[c] 5 mol% of catalyst was used.
[d] 10% of 1,2-dihydronaphthalene was also isolated.

the reaction. This metal-free methodology offers a clean, environmentally friendly, synthetically competitive, and very cheap alternative to the already established use of metal complexes.[17] Another important advantage over other previously reported catalytic methods is that, in our case, the reaction can be performed using easily available polymer-supported *p*-toluenesulfonic acid, which allows the easy isolation of the final product and the reuse of the catalyst.[18]

Experimental Section

General Remarks

All reactions were carried out under air atmosphere without any special precautions. CH_3CN and CH_2Cl_2 were analytical grade and purchased from SDS. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-Plus 300 spectrometer. ^1H NMR spectra (300 MHz) were recorded in $CDCl_3$ and chemical shifts (δ) are reported in ppm from TMS with the residual solvent resonance as internal standard. ^{13}C NMR spectra (75.4 MHz) were measured using $CDCl_3$ as the solvent and the internal standard. GC-MS was performed on an HP 6890N/5973. HR-MS was carried out on a Micromass Autospec spectrometer. *p*-Toluenesulfonic acid monohydrate (PTS) reagent grade (98%), and *p*-toluenesulfonic acid, polymer-bound (macroporous, 30–60 mesh, loading: 2.0 mmol g^{-1}) were purchased from Aldrich. Other chemicals were purchased from Acros, Fluka and Aldrich and used as received.

General Procedure for Reaction of Alcohols 1 with Nucleophiles 2–8 Catalyzed by Polymer-Bound PTS

To a mixture of the corresponding alcohol **1** (1 mmol) and polymer-bound PTS (25 mg, 0.05 mmol) in CH_3CN (5 mL), or alternatively, polymer-bound PTS (50 mg, 0.1 mmol) in CH_2Cl_2 (5 mL), was added the corresponding nucleophile **2–8** (1.2 mmol for allyl alcohols **1a–f** or 2 mmol for benzyl alcohols **1g–j**). The reaction mixture was stirred at room temperature or at reflux (see reaction conditions noted in the text) and the completion of the reaction was monitored by GC-MS. The mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc) to afford the corresponding final product.

Characterization data for **9–15** are listed in the Supporting Information.

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[14] No reaction was observed in DMSO, THF and DMF. In CH_3CN the Ritter-type product *N*-(1-*p*henylethyl)-acetamide was also generated. Details will be given in a future paper.

[15] In some cases, we have observed by GC-MS analysis the formation of the corresponding symmetrical ether.

[16] 1,3-Diphenylbut-1-ene should be formed by the reaction of styrene and phenylethyl cation, and subsequent elimination of a proton, see ref.[7]

[17] PTS, reagent grade, 98%: 2 €/mol (Aldrich ref. 161993); indium(III)chloride, 98%: 1084 €/mol (Aldrich ref. 334065).

[18] In related catalytic reactions with metallic Lewis acids, the possibility of *in situ* formation of small amounts of Brønsted acids, which could also catalyze the process, should be taken into consideration. This possibility has also been suggested by other authors, see: G. Dyker, E. Muth, A. S. K. Hashmi, L. Ding, *Adv. Synth. Catal.* **2003**, *345*, 1247–1252; see also ref.[10] of Campagne's paper here cited in ref.[5] and ref.[10] of Baba's paper here cited in ref.[9b]

