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Metal-Free Catalytic Nucleophilic Substitution of Propargylic Alcohols

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Dedicated to Professor Steven V. Ley on the occasion of his 60th birthday

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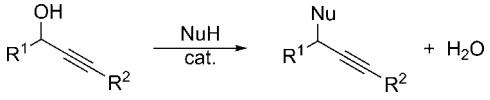
Organic acids such as PTS efficiently catalyze direct nucleophilic substitutions of the hydroxy groups of propargylic alcohols with a large variety of carbon- and heteroatom-centered nucleophiles. Reactions can be conducted under mild conditions and in air without the need for dried solvents. Reactions on multigram scales are also possible.

Introduction

Substitution of a hydroxy group in an alcohol by a nucleophile usually requires the transformation of the hydroxy group into a good leaving group,[1] and the development of new methods for the direct substitution of alcohols is one of the most challenging goals in organic chemistry. In particular, propargylic substitution of hydroxy groups by nucleophiles is a powerful reaction, as the products obtained in these processes are highly interesting building blocks that have been widely used in complex natural product synthesis. The extensive work developed by Nicholas in this area is particularly noteworthy.[2] However, the fundamental drawback of this and other recent related methodologies is that these processes require the use of stoichiometric amounts of cobalt or chromium complexes.[3] Very recently, a few catalytic methodologies for the direct substitution of hydroxy groups of propargylic alcohols[4] in the presence of ruthenium[5] or rhenium[6,7] catalysts have been reported. The major limitation of these processes is that the metallic catalysts employed are expensive and/or not easily available. Furthermore, the reaction is generally limited to terminal and/or secondary propargylic alcohols in the case of the ruthenium catalysts[8] and to internal alkynes in the case of rhenium catalysts. So far, no general method for catalytic propargylic substitution has been reported (Scheme 1).



Scheme 1. Direct propargylic substitution of alkynols.

Results and Discussion

Firmly convinced by the potential of this reaction in organic synthesis, we initiated a project directed towards the identification of new catalysts for the direct propargylic substitution of propargylic alcohols. We thus report here that simple organic acids such as *p*-toluenesulfonic acid monohydrate (PTS) are efficient catalysts of propargylic substitutions with a large variety of heteroatom- and carbon-centered nucleophiles.

Our studies started with the model reaction between alkynol **1a** and ethanol as nucleophile (3 equiv.), with screening of various catalyst systems and use of acetonitrile as solvent at reflux in all cases. Taking advantage of our experience in the use of dioxomolybdenum complexes as catalysts[9] and in view of the similarities of these complexes with the rhenium catalyst used by Toste in related propargylic substitutions,[6] we firstly attempted the reaction in the presence of 5 mol-% of dichlorodioxomolybdenum complexes (Table 1, Entries 1 and 2). Gratifyingly, the reaction proceeded to completion in 1 h, affording the desired ether **2a** in quantitative yield. To check the effectiveness of the catalyst, we ran the reaction in the absence of catalyst, but no formation of compound **2a** was observed after 24 h and the starting material was recovered unchanged (Table 1, Entry 3). These positive findings tempted us to try the catalytic reaction with other Lewis acids such as $InCl_3$, $AlCl_3$, and $CeCl_3$ (5 mol-%) (Table 1, Entries 4–6). In the first case we found complete conversion into the ether **2a** in 1 h. With

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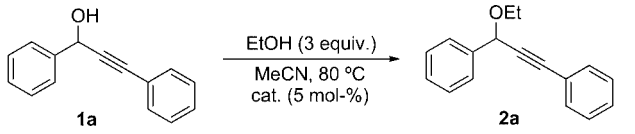
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

use of 5 mol-% of $AlCl_3$ the reaction had, after 24 h, given a mixture of ether **2a** and starting material **1a** (80:20 ratio determined by ^1H NMR analysis of the crude product of the reaction; Table 1, Entry 5). With $CeCl_3 \cdot 7H_2O$, after 36 h the reaction had produced 34% of **2a** and 12% of the corresponding oxidized ketone, along with 53% of the starting alkynol **1a** (Table 1, Entry 6). All these encouraging results led us to consider the possibility of using simple organic acids as catalysts. Evidently, if this process proceeded it would be a significant advance as it would avoid the use of potentially toxic metallic species. To our delight, when we performed the above reaction in the presence of PTS (*p*-toluenesulfonic acid monohydrate) or CSA (camphorsulfonic acid) (5 mol-%) as catalysts, the reactions cleanly afforded the propargylic ether **2a** in short times and in essentially quantitative yields (Table 1, Entries 7–9). Moreover, dilute HCl (10 mol-%) also catalyzes this transformation (Table 1, Entry 10). It should be remarked that, in these cases, the reaction is tolerant of air and moisture and so can be conducted in an open flask and with direct use of solvent without any previous drying treatment.

Table 1. Catalyst screening for ethyl etherification.[a]

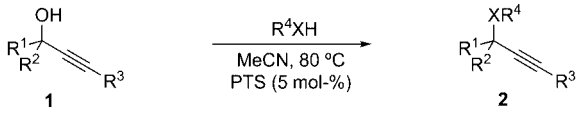


Entry	Catalyst	*t* [h]	mol-% catalyst	%**2a**[b]
1	$MoO_2Cl_2(dmf)_2$	1	5	>95
2	$MoO_2Cl_2(dmso)_2$	1	5	>95
3	–	24	–	0
4	$InCl_3$	1	5	>95
5	$AlCl_3$	24	5	80
6	$CeCl_3 \cdot 7H_2O$	36	5	34
7	PTS	1	5	>95
8	PTS	4	5	>95[c]
9	CSA	1	5	>95
10	HCl, 1M	4	10	>95

[a] Reaction conditions: MeCN, 80 °C, EtOH (3 equiv.). [b] Yields were determined by ^1H NMR or GC-MS analysis of the crude reaction mixture. [c] Run at room temp.

In order to check the scope of this process, we performed a set of experiments with several propargylic alcohols **1** and different heteroatom-centered nucleophiles, such as alcohols, thiols, amines, and amides in the presence of PTS (5 mol-%) as catalyst (Table 2).[10] Starting from alkynols **1a**–**c**, each containing an internal alkyne group, the reactions gave the expected substitution compounds **2** in high yields and short reaction times (*ca.* 1 h). We have applied this methodology to the synthesis of propargylic ethers (Entries 1–3, 6–10 and 12–14), thioethers (Entries 4 and 15),

Table 2. Propargylic substitution of alkynols **1** with heteroatom nucleophiles.[a]

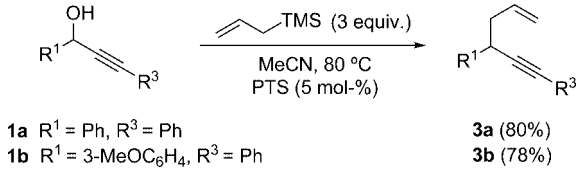


Entry	Alkynol	R^1	R^2	R^3	R^4XH	Product	Yield (%)[b]
1	**1a**	Ph	H	Ph	EtOH	**2a**	80
2					$PhCH_2OH$	**2b**	76
3					$CH_2=CHCH_2OH$	**2c**	74
4					$CH_3(CH_2)_{11}SH$	**2d**	80
5					$PhSO_2NH_2$	**2e**	67
6	**1b**	3-$MeOC_6H_4$	H	Ph	MeOH	**2f**	75
7					$CH_2=CHCH_2OH$	**2g**	78
8					$MeOCH_2CH_2OH$	**2h**	76
9					(–)menthol	**2i**	60[c]
10					$CH{\equiv}CCH_2OH$	**2j**	72
11					4-$NO_2C_6H_4NH_2$	**2k**	73
12	**1c**	Ph	H	Bu	EtOH	**2l**	81
13					$CH_2=CHCH_2OH$	**2m**	75
14					$ClCH_2CH_2OH$	**2n**	63
15					$CH_3(CH_2)_{11}SH$	**2o**	83
16					$PhSO_2NH_2$	**2p**	66
17	**1d**	Ph	H	H	EtOH	**2q**	58[d]
18					$CH_3(CH_2)_{11}SH$	**2r**	52[d]
19	**1e**	2-naphthyl	H	H	MeOH	**2s**	75[e]
20	**1f**	Ph	Me	Ph	EtOH	**2t**	90[f]
21	**1g**	Me	Me	Ph	EtOH	**2u**	86
22					$CH_3(CH_2)_{11}SH$	**2v**	70
23	**1h**	Ph	Ph	Ph	EtOH	**2w**	75[f][g]

[a] General reaction conditions: 3 equiv. of nucleophile in MeCN at reflux for 1 hour. [b] Isolated yields after chromatography based on starting alkynol **1**. [c] Obtained as a *ca.* 2:1 mixture of diastereoisomers. [d] 24 h were required for complete conversions. Small amounts (<15%) of bis(1-phenylprop-2-ynyl) ether and cinnamaldehyde were also isolated. [e] 4 h were required for complete conversion. Small amounts (<10%) of bis[1-(2-naphthyl)prop-2-ynyl] ether were also isolated. [f] Run at room temp. [g] A 10% yield of β-phenylchalcone was also isolated.

amines (Entry 11), and amides (Entries 5 and 16). To our delight, the reactions also proceeded effectively with terminal alkynols (**1d**, **1e**), though significantly longer reaction times (4–24 hours) were required for complete conversions. This methodology is not limited to secondary benzylic substrates, as shown by the reactions between tertiary alcohols **1f** or **1g** and ethanol or dodecanethiol (Entries 20–22). Interestingly, the reactivity of highly activated tertiary alkynols such as **1h** is complicated by the competing Meyer–Schuster rearrangement[11] and isolation of ether **2w** required strict control of the temperature (RT), the reaction time (30 min), and neutralization prior to the purification step (Entry 23).[12] Moreover, when the starting material was enantiomerically enriched propargylic alcohol **1a** (94% *ee*)[13] the corresponding ethyl ether **2a** was obtained in a racemic form. All these results seem to indicate that the reaction proceeds through the formation of a stabilized carbonium intermediate.[14]

The reactions described above for the metal-free catalytic synthesis of heteroatom-substituted propargylic compounds undoubtedly represent a significant achievement as they provide a competitive method to the known strategies for the synthesis of these kinds of compounds. From the point of view of organic synthesis, however, a major challenge is the creation of new carbon–carbon bonds. With this idea in mind, we turned our attention to the achievement of direct propargylic substitution of hydroxy groups with carbon-centered nucleophiles. We first tried allyltrimethylsilane as nucleophile and were pleased to find that the reaction took place efficiently, affording the corresponding 1,5-enynes **3** in good yields (Scheme 2). This catalytic reaction provides



Scheme 2. Propargylation of alkynols **1** with allyltrimethylsilane.

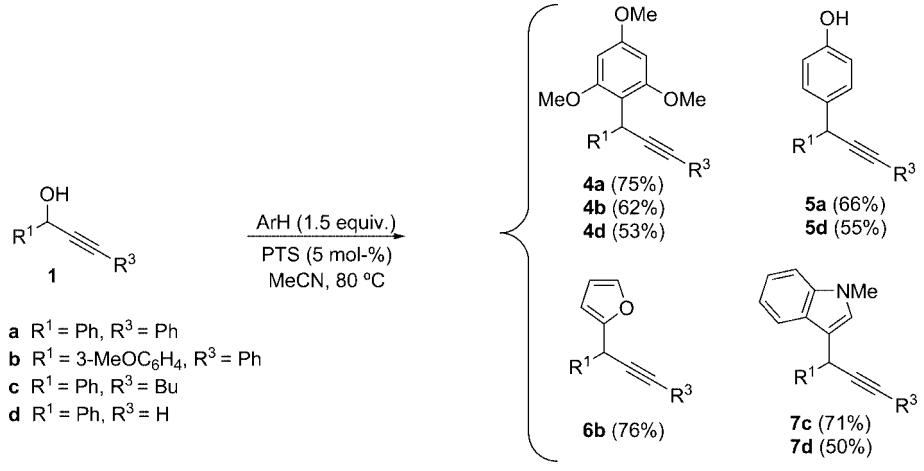
an attractive alternative for the construction of sp^3–sp^3 carbon–carbon bonds without use of any metallic catalyst.

We then examined the propargylation of alkynols **1** with aromatic and heteroaromatic compounds. We were pleased to find that the presence of 5 mol% of PTS efficiently catalyzed the aromatic propargylation (Scheme 3). The reaction proceeded efficiently with electron-rich arenes such as 1,3,5-trimethoxybenzene, affording compounds **4**. Propargylation of phenol took place without observation of any *O*-alkylation competitive process and through the *para* position,[15] giving rise to *p*-substituted phenols **5**. Heteroaromatic compounds such as furan and *N*-methylindole could also be propargylated with complete regioselectivity through the use of this catalytic system to provide functionalized heterocycles **6**–**7**.

Finally, in order to check whether this simple experimental approach could be applied to multigram synthesis, 6.8 g of **2f** (80% isolated yield) were easily prepared in one batch from 8.1 g (34 mmol) of alkynol **1b**.[16] This experiment demonstrates that the method is also of interest for the preparation of at least moderate amounts of these interesting compounds in a practicable manner.

Conclusions

In summary, we have found that simple organic acids catalyze the direct propargylic substitution of hydroxy groups by a range of heteroatom- and carbon-centered nucleophiles.[17] The reaction is tolerant of air and moisture and gives water as the only byproduct. This metal-free strategy represents a clean, environmentally friendly, and synthetically competitive alternative to the already established use of metal complexes. We have also demonstrated that this method is amenable to large scale synthesis. As the reaction implies the use of very simple starting materials and catalysts, and since the products obtained are of great interest, this methodology may be expected to find wide application in organic synthesis.[18] Current studies are being directed to investigation of the reaction's scope, mechanism, limita-



Scheme 3. Propargylation of alkynols **1** with aromatic and heteroaromatic compounds.

tions, and applicability to the synthesis of some natural products, together with the development of an asymmetric version.

Experimental Section

General Procedure for PTS-Catalyzed Nucleophilic Substitutions of Alkynols 1: A flask was charged with alkynol **1** (1 mmol), MeCN (analytical grade, 5 mL) and the nucleophile (3 mmol for heteroatom nucleophiles and allyltrimethylsilane and 1.5 mmol for aromatics). PTS (5 mol-%) was added and the flask was heated at 80 °C. Reaction mixtures were maintained at reflux until completion as judged by TLC or GC-MS analysis of the mixture. The solvent was removed under reduced pressure and the residue was then purified by column chromatography (silica gel; hexane/ethyl acetate), affording the corresponding product.

Supporting Information (for details see the footnote on the first page of this article): Experimental procedures and spectroscopic data for all compounds and copies of the NMR spectra of the crude product obtained from the multigram reaction between **1b** and methanol.

Acknowledgments

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[1] O. Mitsunobu, in: *Comprehensive Organic Synthesis*, vol. 6 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, pp. 22–28 and 65–76.

[2] a) K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207–214; b) A. J. M. Caffyn, K. M. Nicholas, in: *Comprehensive Organometallic Chemistry II*, vol. 12 (Eds.: E. W. Abel, G. A. Stone, G. Wilkinson), Pergamon, New York, **1995**, chapter 7.1; c) B. J. Teobald, *Tetrahedron* **2002**, *58*, 4133–4170.

[3] T. J. Müller, *Eur. J. Org. Chem.* **2001**, 2021–2033.

[4] Interesting related Lewis acid-catalyzed propargylic substitution reactions of silyl propargyl ethers have recently been published: a) T. Ishikawa, M. Okano, T. Aikawa, S. Saito, *J. Org. Chem.* **2001**, *66*, 4635–4642; b) T. Ishikawa, S. Manabe, T. Aikawa, T. Kudo, S. Saito, *Org. Lett.* **2004**, *6*, 2361–2364.

[5] a) Y. Nishibayashi, I. Wakiji, M. Hidai, *J. Am. Chem. Soc.* **2000**, *122*, 11019–11020; b) Y. Nishibayashi, I. Wakiji, Y. Ishii, S. Uemura, M. Hidai, *J. Am. Chem. Soc.* **2001**, *123*, 3393–3394; c) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846–11847; d) Y. Nishibayashi, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 6060–6061; e) V. Cadierno, J. Díez, S. E. García-Garrido, J. Gimeno, *Chem. Commun.* **2004**, 2716; f) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uemura, *Chem. Eur. J.* **2005**, *11*, 1433–1451.

[6] a) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077; b) M. R. Luzung, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 15760–15761; c) J. J. Kennedy-Smith, L. A. Young, F. D. Toste, *Org. Lett.* **2004**, *6*, 1325–1327; d) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R. Holman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501–2504.

[7] After the submission of this paper, a related gold-catalyzed reaction appeared see: M. Georgy, V. Boucard, J.-C. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181.

[8] The ruthenium-catalyzed propargylic substitutions are believed to proceed via allenylidene complex intermediates and so terminal alkynes are required. For an interesting mechanistic study, see: a) S. C. Ammal, N. Yoshikai, Y. Inada, Y. Nishibayashi, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 9428–9438. However, a few examples involving the reactions of internal alkynes have been reported: b) Y. Inada, Y. Nishibayashi, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 15172–15173; c) Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai, S. Uemura, *Angew. Chem.* **2003**, *115*, 1533–1536; *Angew. Chem. Int. Ed.* **2003**, *42*, 1495–1498; d) E. Bustelo, P. H. Dixneuf, *Adv. Synth. Catal.* **2005**, *347*, 393–397.

[9] a) R. Sanz, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synthesis* **2002**, 856–858; b) R. Sanz, J. Escribano, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synthesis* **2004**, 1629–1632; c) R. Sanz, J. Escribano, Y. Fernández, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synlett* **2005**, 1389–1392.

[10] Although the reactions were conducted with 3 equiv. of the corresponding nucleophile and 5 mol-% of PTS in acetonitrile at reflux, we have observed that the reaction also takes place at room temperature, with the catalyst loading decreased to 1 mol-% and with use of only 1 equiv. of nucleophile. Under these conditions longer reaction times were required for complete conversions.

[11] The Meyer–Schuster rearrangement usually needs strong acids or metals as catalysts and elevated temperatures: a) S. Swaninathan, K. V. Narayanan, *Chem. Rev.* **1971**, *71*, 429–438; b) C. Y. Lorber, J. A. Osborn, *Tetrahedron Lett.* **1996**, *37*, 853–856; c) T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Tetrahedron Lett.* **2002**, *43*, 7531–7533.

[12] Use of longer reaction times at room temp. (48 h) resulted in complete conversion of the initially formed ether **2w** to the corresponding rearranged α,β-unsaturated carbonyl derivative (Meyer–Schuster rearrangement).

[13] Enantio-enriched **1a** was prepared in accordance with: M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai, D. B. Cardin, *Tetrahedron* **1984**, *40*, 1371–1380.

[14] For a review on alkynyl carbenium ions see: S. M. Lukyanov, A. V. Koblik, L. A. Muradyan, *Russ. Chem. Rev.* **1998**, *67*, 817–856.

[15] PPTS-catalyzed propargylation of phenols and naphthols results in the formation of benzopyran derivatives: W. Zhao, E. M. Carreira, *Org. Lett.* **2003**, *5*, 4153–4154.

[16] ^{1}H and ^{13}C NMR spectra of the crude product obtained from this multigram reaction are included in the Supporting Information.

[17] Other nucleophiles used in related works, such as diphenylphosphane oxide or enol silyl ethers, are being studied in our laboratories; a full detailed account will be provided in due course.

[18] For a patent on the direct propargylic substitution in the presence of rhenium complexes as catalysts, see: F. D. Toste, U. S. Pat. Appl. Publ. **2004**, US2004181094 [*Chem. Abstr.* **2004**, *141*, 277341].

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