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Hydroalkoxylation of non-activated olefins catalysed by Lewis superacids in alcoholic solvents: an eco-friendly reaction

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Abstract—Lewis superacids such as tin(IV) triflate catalyse the intermolecular addition of primary alcohols to non-activated olefins under mild conditions.

Electron-rich C–C multiple bonds such as alkynes,[1] allenes,[2,3] and in some cases alkenes[4] can be activated by metal-based catalysts and undergo functionalisation by heteronucleophiles. To facilitate the nucleophilic attack to alkenes, a polarisation of the double bond is often required, for example, by conjugation with a carbonyl function,[5,6] another double bond,[7] or an arene.[8,9] The lack of reactivity of non-activated olefins towards nucleophiles, and particularly towards oxygenated nucleophiles, and their activation by metal-based catalysts is still a challenge in synthetic organic chemistry.

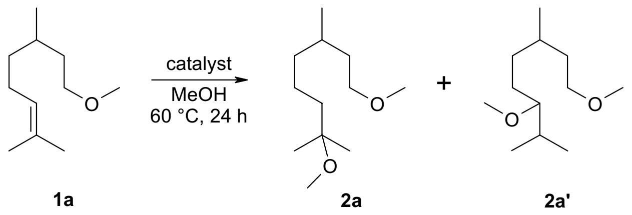
The intramolecular hydroalkoxylation of non-activated δ- and γ-hydroxy olefins to cyclic ethers has been recently reported using catalytic amounts of triflic acid,[10] Al(III) or Sn(IV) triflates,[11,12] and Pt^{II}-complexes.[13]

A combined Pd^{II}/Cu^{II} system has been reported to catalyse the hydroalkoxylation of *ortho*-vinylphenol via a Pd–H generated in the presence of 1-phenylethanol as hydride source.[14] The formation of ethers by intermolecular addition of alcohols to non-activated olefins generally requires excess protic acids, or the use of zeolites.[15,16] Intermolecular hydroalkoxylation of non-activated olefins leading to the corresponding ethers can be catalysed by Ru^{III}-complexes in the presence of Ag^{I}-salts,[17] Pd^{II}-salts in the presence of $CuCl_2$,[18] and Pd^0-complexes.[19]

The absence of straightforward catalytic methods for the hydroalkoxylation of non-activated olefins prompted us to examine the efficiency of Lewis superacids as catalysts. We mainly focused on natural terpene derivatives as starting materials and common alcohols as the solvents.

A first screening of the catalytic activity of a selection of Lewis and Bronsted acid catalysts for the functionalisation of racemic methyl citronellyl ether **1a**, chosen as a model substrate, was carried out in methanol (Scheme 1).

In the absence of catalyst, the starting material was quantitatively recovered unchanged (Table 1, entry 1). The product selectivity **2a**/**2a′** refers to the ratio between the product of the expected Markovnikov-type addition **2a** and the *anti* Markovnikov-type product **2a′**.



Scheme 1.

Keywords: Hydroalkoxylation; Lewis acids; Non-activated olefins; Tin triflate; Catalysis; Odorants.

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Table 1. Catalyst screening in the hydroalkoxylation of methyl citronellyl ether **1a** in MeOH, 24 h at 60 °C

Entry	Catalyst	mol %	Conversion (%)	Yield[a]	**2a/2a′**
1	None	—	0	—	—
2	TfOH	5	22	13	80/20
3	$HNTf_2$	5	25	23	95/5
4	$Sn(OTf)_4$	5	70	54	84/16
5	$Sn(NTf_2)_4$	5	47	45	91/9
6	$Al(OTf)_3$	5	31	9	89/11
7	$In(OTf)_3$	5	39	29	76/24
8	$Sn(OTf)_2$	5	50	28	95/5
9	$Pd(CH_3CN)·2OTf$	5	5	<5%	—
10	$Al(OTf)_3$	20	45	39	85/15
11	$Sn(OTf)_4$	20	79	77	84/16

[a] Hydroalkoxylation yield, determined by ^{1}H NMR.

Heating olefin **1a** in anhydrous methanol at 60 °C in the presence of 5 mol % HOTf or $HNTf_2$ led only to 22–25% conversion after 24 h, yielding 13–23% of hydroalkoxylated products **2a** + **2a′** (entries 2 and 3). The reaction was more efficient when catalysed by metal-based Lewis superacids such as Sn(IV) triflate (70% conversion, entry 4) and Sn(IV) triflimidate (47% conversion, entry 5). Both catalysts were prepared by an electrochemical procedure from metallic tin and HOTf or $HNTf_2$.[20] Al(III) and In(III) triflates led to similar reaction profiles albeit with moderate conversions (entries 6 and 7). Sn(II) triflate qualitatively reproduced the result obtained with Sn(IV) triflate but in lower yield (entry 8); the electrophilic activation of the doubly charged tin cation was probably too weak to efficiently allow the attack of methanol. The cationic Pd(II) complex $Pd(CH_3CN)·2OTf$, formed by treatment of $Pd(CH_3CN)·Cl_2$ with 2 equiv of AgOTf, was not active in this reaction (entry 9). In general, the regioselectivity was strongly in favour of the Markovnikov-type product **2a**.

In each case, additional reaction time did not allow to increase the conversion. However, a higher catalyst ratio resulted in the enhancement of both the yield and the conversion with Al(III) triflate and Sn(IV) triflate (entries 10 and 11), the yields rising from 9% to 39% and from 54% to 77%, respectively. To check if the catalyst could suffer from rapid deactivation under the reaction conditions, we tried to add it portionwise to the reaction medium, unfortunately without significant improvement. Having identified Sn(IV) triflate as the best catalyst for the hydroalkoxylation of **1a**, we further screened a selection of solvents. Running reactions in methanol remained the best choice, since with 10 equiv of MeOH in acetonitrile, toluene or dichloroethane, the rates of conversion remained below 50%. Under reaction conditions inspired by those of Hartwig and coll. (1 mol % catalyst in toluene),[21] HOTf remained poorly active in the hydromethoxylation reaction, the conversion remaining below 20%.

We next extended the substrate scope of this hydroalkoxylation reaction catalysed by Sn(IV) triflate (Table 2). In the terpenoid family, the hydroalkoxylation of trisubstituted double bonds such as in the case of citronellol **1b** (entry 2), limonene **1c** (entry 3), citronellene **1d** (entry 4), and α-pinene **1e** (entry 5) was achieved in 24 h in the presence of 5 mol % catalyst in 15–70% yields. Hydromethoxylated products were the only products isolated after the reaction, along with some unconverted starting material. Conversions were in the range of 33–100% and yields were sometimes lowered by a partial evaporation of the volatile products during solvent removal and possible degradation of the starting material. The free hydroxyl group of citronellol **1b** did not modify the course of the reaction, and the methoxylated compound **2b** was formed regiospecifically as the only product in 50% yield. With limonene **1c**, the reaction yielded 53% of the mono-hydromethoxylated product **2c** corresponding to the functionalisation of the isoprenyl moiety. Additionally, doubly methoxylated product was formed in 26% yield from the hydromethoxylation of both double bonds of **1c**. In the case of citronellene **1d**, the terminal double bond was not modified. During the hydroalkoxylation process, bicyclic α-pinene rearranged to the terpineol derivative through ring-opening of the four-membered ring.[22]

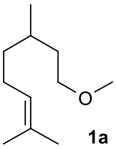
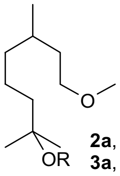
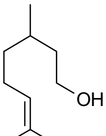
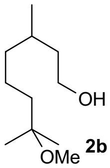
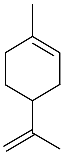
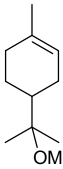
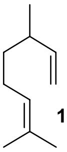
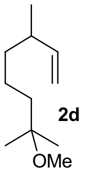
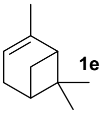
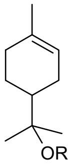
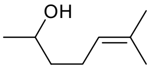
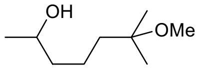
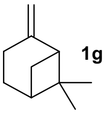
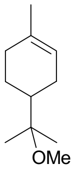
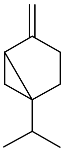
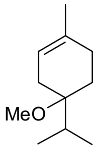
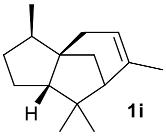
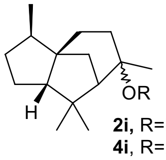
The reactivity of the double bond of substrate **1f** was interesting, because of the possibility of an intramolecular 6-*endo*-trig cycloisomerisation with the secondary alcohol function. However, after 24 h at 60 °C in MeOH, a conversion of 53% was reached and only the hydromethoxylated product **2f** was regioselectively formed in 32% yield (entry 6). The competition between the addition of MeOH and the intramolecular addition of the alcohol was thus in favour of the intermolecular process.

Examples of functionalisation of exocyclic double bonds were carried out with substrates **1g** and **1h**, which were converted, in methanol, to the corresponding methoxylated and rearranged derivatives **2e** and **2h** in 61% and 70% yields, respectively (entries 7 and 8). The terminal position of the double bond, more available to bind the bulky $Sn(OTf)_4$ catalyst, afforded higher conversions as compared to those obtained with **1e**.

Disubstituted internal olefins such as norbornadiene, norbornene and 2-acetylnorbornene, as well as cyclooctene and cyclooctadiene were unreactive, and 1,1-diphenylethylene yielded only 7% of methoxylated product (not shown). Replacing methanol by ethanol and 1-butanol allowed to heat the reaction at higher temperatures (from 78 °C to 117 °C) but did not afford better yields, although conversions were slightly improved (compare entries 1, 5 with EtOH and *n*-BuOH). The hydrobutoxylated products **4a** and **4e** were formed as the sole products in 40% and 49% yields, when the reactions were carried out in 1-butanol at 117 and 80 °C, respectively.

The synthesis of the methoxysesquiterpene 8-methoxycedrane **2i** was further envisaged as a synthetic application of this methodology. This compound is used in fragrance industry under the tradenames Cedramber® and Cedranfix® for its cedarwood and amber olfactory notes.[23] (−)-α-Cedrene **1i** was submitted to the hydro-

Table 2. Hydroalkoxylation of non-activated olefins catalysed by Sn(IV) triflate (5 mol %) in alcoholic solvent 24 h

Entry	Substrate	Solvent	*T* °C	Conversion (%)	Major product	Yield[a]	Regioselectivity[b]
1	 **1a**	MeOH EtOH *n*-BuOH	60 78 117	70 44 100	 **2a**, R=Me **3a**, R=Et **4a**, R=*n*-Bu	54 43 40	84/16 100/0 100/0
2	 **1b**	MeOH	60	50	 **2b**	50	100/0
3	 **1c**	MeOH	60	90	 **2c**	53[c]	95/5
4	 **1d**	MeOH	60	33	 **2d**	24	95/5
5	 **1e**	MeOH EtOH *n*-BuOH	60 78 80	70 63 80	 **2e**, R=Me **3e**, R=Et **4e**, R=*n*-Bu	70 15 49	—
6	 **1f**	MeOH	60	53	 **2f**	32	100/0
7	 **1g**	MeOH	60	100	 **2e**	70	—
8	 **1h**	MeOH	60	100	 **2h**	61[d]	—
9	 **1i**	MeOH *n*-BuOH	60 100	0 18	 **2i,** R=Me **4i**, R=*n*-Bu	— 5[e]	 —

[a] Hydroalkoxylated products, determined by ^{1}H NMR.

[b] Ratio **2**/**2′**, **3**/**3′**, or **4**/**4′** determined by GC-FID.

[c] Bis-hydromethoxylated product was also formed in 26% yield.

[d] Sum of **2h** + isomeric **2e** (1:1).

[e] Two diastereomers.

alkoxylation catalysed by $Sn(OTf)_4$, but remained unchanged even after 4 days at 60 °C in MeOH. In the presence of $HNTf_2$, no methoxycedrane **2i** was formed. However, in 1-butanol at 100 °C, the expected 8-butoxycedrane **4i** was formed in 5% yield after 5 days of reaction, 82% of the starting material being recovered (entry 9). Steric hindrance resulting from the interaction of the bulky $Sn(OTf)_4$ with such polycyclic and conformationally strained substrate can explain the lack of reactivity of **1i**.

In summary, we describe herein a simple methodology to add primary alcohols to non-activated di- or trisubstituted double bonds. This hydroalkoxylation reaction proceeds in alcoholic solvent at moderate temperature in the presence of 5 mol % of metallic triflates, preferably tin(IV) triflate, without the need of ligands, additives or co-catalysts, and affords the expected ethers in moderate yields.[25] The Markovnikov-type adducts are formed with regioselectivities of 84–100%. These features, for example, renewable chemicals from bioresources, safe solvent and catalytic reagents, are of prime interest in the development of sustainable synthetic processes in chemistry.[24]

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25. Representative procedure: Hydromethoxylation of **1a**. $Sn(OTf)_4$ (36 mg, 0.05 mmol) and methyl citronellyl ether **1a** (170 mg, 1.0 mmol) are introduced in a Schlenck tube. Anhydrous methanol (1 mL) is added and the mixture is degassed under vacuum and heated at 60 °C under a nitrogen atmosphere. After 24 h, the mixture is purified by flash chromatography over silica gel using a gradient cyclohexane to cyclohexane/AcOEt 1:1 as eluent. For example, data for 2,8-dimethoxy-2,6-dimethyloctane **2a**: colourless liquid (110 mg, 54% yield). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): 3.40 (t, $J = 6.6$ Hz, 2H); 3.33 (s, 3H); 3.17 (s, 3H); 1.80–1.00 (m, 15H); 0.89 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): 74.6; 71.2; 58.6; 49.1; 40.1; 37.7; 36.7; 30.2; 25.0; 25.0; 21.2; 19.6. MS (EI, 70 eV, selected ions, *m/z*): 202 (0) $[M]^{+\cdot}$; 187 (4) $[M-15]^{+\cdot}$; 138 (11); 123 (29); 109 (14); 95 (50); 81 (95); 73 (100); 55 (94).