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$FeCl_3$-catalyzed functionalization of monoterpenes via hydroalkylation of unactivated alkenes

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ABSTRACT

Monoterpenes such as α-pinene, β-pinene, limonene and isolimonene undergo smooth hydroalkoxylation in the presence of 20 mol % of $FeCl_3$ under mild reaction conditions to produce a wide range of the corresponding ethers in excellent yields and with high selectivity.

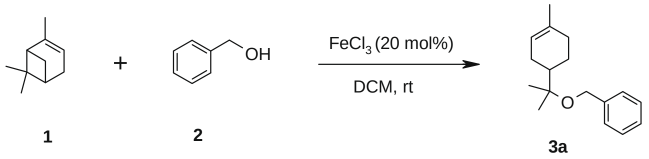
Electron-rich C–C multiple bonds such as alkynes,[1] allenes,[2,3] and in some cases alkenes[4] can be activated by metal-based catalysts and undergo functionalization by heteronucleophiles. The lack of reactivity of non-activated olefins towards nucleophiles, in particular, oxygenated nucleophiles, 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,[5] Al(III) or Sn(IV) triflates,[6,7] and Pt(II)-complexes.[8] The formation of ethers by intermolecular addition of alcohols to non-activated olefins generally requires excess of protic acids or the use of zeolites.[9,10] Intermolecular hydroalkoxylation of non-activated olefins leading to the corresponding ethers has been reported using various expensive metal catalysts such as Ru(III)-complexes in the presence of Ag(I)-salts,[11] Pd(II)-salts in the presence of $CuCl_2$[12] and Pd(0)-complexes.[13] The absence of straight forward catalytic methods for the hydroalkoxylation of non-activated olefins prompted us to examine the efficiency of Lewis super acids as catalysts.

In the recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst to perform many useful organic transformations under mild reaction conditions.[14] Moreover, iron-salts are inexpensive, easy to handle and are environmentally friendly. However, there have been no previous reports on the direct coupling of alcohols with monoterpenes such as α-pinene, β-pinene, limonene and isolimonene using $FeCl_3$ as a catalyst.

In this Letter, we report a direct $FeCl_3$-catalyzed hydroalkoxylation of monoterpenes such as α-pinene, β-pinene, limonene and isolimonene with alcohols under mild conditions to produce a wide range of the corresponding ethers in excellent yields. We first attempted the hydroalkoxylation of α-pinene (**1**) with benzyl alcohol (**2**) by using 20 mol % anhydrous $FeCl_3$ in dichloromethane. The reaction went to completion in 1.5 h at room temperature giving product **3a** in 80% yield (Scheme 1).

Similarly, α-pinene reacted smoothly with various alcohols such as allyl, homoallyl, propargyl, homopropargyl and phenethyl to produce the corresponding ethers (Table 1, entries **b**–**f**). Other alcohols such as primary, secondary, tertiary and cyclic also participated well to produce the corresponding ethers in good yields (Table 1, entries **g**–**j**).

Like α-pinene, β-pinene also worked effectively in this reaction and the resulting products are the same (Table 1, entries **k** and **m**) as α-pinene. We also examined the reactivity of limonene and isolimonene with benzyl and aliphatic alcohols. Interestingly, these substrates also gave the corresponding ethers in high yields (Table 1, entries **n**–**s**).



Scheme 1.

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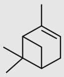
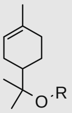
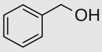
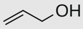
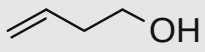
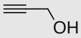
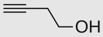
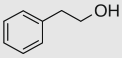
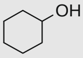
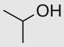
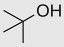
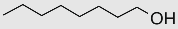
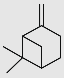
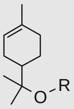
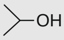
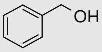
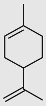
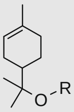
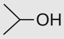
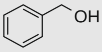
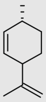
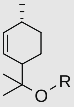
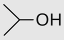
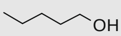
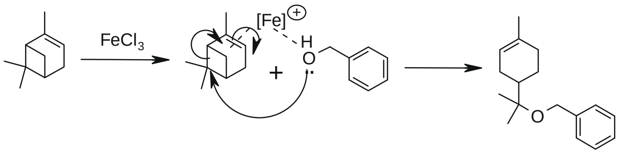
Table 1
FeCl3-catalyzed hydroalkoxylation of unactivated olefins

Entry	Alkene	Alcohol	Product[a]	Time (h)	Yield[b] (%)
					
a			R = benzyl	1.5	80
b			R = allyl	2.0	90
c			R = homoallyl	2.5	92
d			R = propargyl	2.0	80
e			R = homopropargyl	1.5	70
f			R = 2-phenethyl	1.5	75
g			R = cyclohexyl	1.0	85
h			R = isopropyl	1.2	90
i			R = *t*-butyl	1.5	82
j			R = *n*-octyl	1.2	86
					
k		CH_3OH	R = methyl	1.0	80
l			R = isopropyl	1.2	84
m			R = benzyl	1.4	78
					
n			R = isopropyl	1.2	87
o		CH_3OH	R = methyl	1.2	80
p			R = benzyl	1.4	82
					
q		CH_3OH	R = methyl	2.2	80
r			R = isopropyl	2.1	76
s			R = *n*-pentyl	2.5	70

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.

Mechanistically, the reaction may proceed via the activation of alkene by metal catalyst and a subsequent migration of double bond through opening of the four-membered ring with appropriate alcohol (Scheme 2). In general, the regioselectivity was strongly in favour of the Markovnikov-type product. In case of limonene and isolimonene, the metal chooses the terminal alkene and the attack



Scheme 2.

of nucleophile follows Markovnikov's rule. Finally monoterpenes were converted into terpinol derivatives.

In the absence of catalyst, the reaction failed to give the desired product. The products were characterized by ^{1}H NMR, IR and mass spectrometry and also by comparison with authentic samples.[15] The advantages of this procedure include mild conditions as well as short reaction times, easy work-up and good yields. There was no considerable difference in yields when comparing α-pinene, β-pinene, limonene and isolimonene. In the case of isolimonene, no racemization was observed. No chlorination of monoterpenes was observed under the reaction conditions. However, aromatic alcohols failed to give the desired product under the reaction conditions. Among various Lewis acids such as $TiCl_4$, $SnCl_4$ and $BF_3.OEt_2$ tested, $FeCl_3$ was found to be superior in terms of conversion. For example, α-pinene and benzyl alcohol in the presence of $TiCl_4$, $SnCl_4$, $BF_3.OEt_2$ and $FeCl_3$ gave the product **3a** in 45%, 52%, 65% and 80% yields, respectively. Furthermore, we have examined the possibility of $FeCl_3$ functioning catalytically or at least less than 20 mol %. Though reactions proceeded with 10 mol % $FeCl_3$, long reaction times (8–12 h) were required to achieve comparable yields. But best results were obtained with 20 mol % of $FeCl_3$. The scope and generality of this process are illustrated with respect to various alcohols and monoterpenes and the results are presented in Table 1.[16]

In summary, anhydrous $FeCl_3$ has proved to be a useful and highly efficient catalyst for the hydroalkoxylation of unactivated alkenes under mild conditions. In addition to its simplicity and efficiency, this method produces alkoxy monoterpenes in excellent yields in short reaction times. This method provides an easy access to a wide range of alkoxy monoterpenes. The use of readily available $FeCl_3$ makes this method simple, convenient, cost-effective and practical.

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16. *General procedure*: To a stirred solution of α-pinene (163 mg, 1.2 mmol) and benzyl alcohol (108 mg, 1.0 mmol) in dichloromethane (4 mL) was added $FeCl_3$ (32 mg, 0.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography to afford pure alkoxy monoterpene derivative. *Spectroscopic data for selected products: 4-(1-(benzyloxy)-1-methylethyl)-1-methyl-cyclohexene* (**3a**): Liquid, IR (KBr): ν 3027, 2966, 2923, 1721, 1604, 1450, 1378, 1249, 1144, 1059, 912, 734, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (s, 6H), 1.23–1.40 (m, 1H), 1.63 (s, 3H), 1.67–2.10 (m, 6H), 4.40 (s, 2H), 5.35 (br s, 1H), 7.14–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 22.5, 22.9, 23.5, 26.4, 30.6, 41.8, 62.6, 120.4, 126.4, 126.6, 127.7, 129.2, 132.5, 133.4; ESI-MS: *m*/*z*: 245 ($M+H^+$), 227, 201, 189, 178, 161, 149, 138. *4-(1-isopropoxy-1-methylethyl)-1-methyl-cyclohexene* (**3h**): Liquid, IR (KBr): ν 2966, 2924, 1723, 1637, 1495, 1451, 1381, 1220, 1060, 1025, 913, 733, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04–1.08 (d, *J* = 2.2 Hz, 6H,), 1.09 (s, 6H), 1.12–1.30 (m, 1H), 1.45–1.58 (m, 1H), 1.62 (s, 3H), 1.66–2.05 (m, 5H), 3.70–3.84 (m, 1H), 5.32 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2, 23.7, 24.1, 24.4, 25.4, 25.6, 27.6, 31.5, 43.4, 63.1, 121.3, 134.4; LC–MS: *m*/*z*: 197 ($M+H^+$), 179, 102, 74, 59. *4-(1-methoxy-1-methylethyl)-1-methyl-1-cyclohexene* (**3k**): Liquid, IR (KBr): ν 2923, 2853, 1645, 1539, 1458, 1376, 1079, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (s, 6H), 1.14–1.33 (m, 1H), 1.59–2.06 (m, 9H), 3.16 (s, 3H), 5.34 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 22.3, 23.3, 23.8, 26.8, 29.6, 31.0, 41.4, 48.6, 120.8, 133.9; LC–MS: *m*/*z*:169 ($M+H^+$), 140, 111.