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Bifunctional Copper Catalysts. A One Step Synthesis of Bicyclic Ethers Starting from α,β-unsaturated Ketones

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***Abstract*:** A new, one pot synthesis of bicyclic ethers starting from α,β-unsaturated ketones containing an additional isolated olefinic bond is proposed. It relies on highly chemoselective hydrogenation of the enone group to the corresponding alcohol in the presence of supported copper catalysts, and on the presence of acidic sites on the catalyst support activating the double bond as a carbocation.
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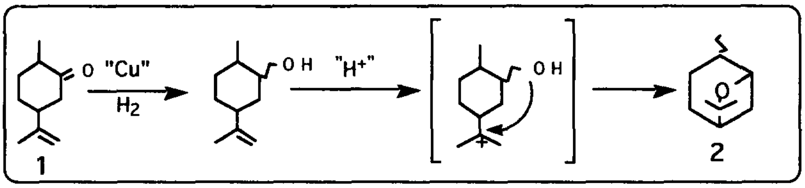
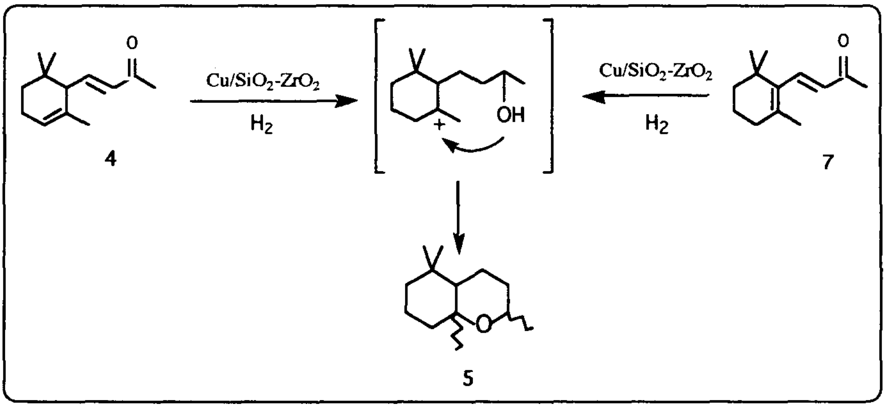
The synthesis of bicyclic ethers, useful intermediates in the fragrance industry, requires a multi step route[1] involving the use of $LiAlH_4$ to carry out the selective hydrogenation step, the ring closure often relying on the use of mineral acids. We recently reported on the use of Cu/SiO_2 in the chemoselective hydrogenation of α,β-unsaturated ketones containing also an olefinic carbon-carbon bond.[2] When silica was used as the catalyst support, quantitative yields of saturated ketones were obtained also in the case of α- and β-ionone. An exception was represented by carvone **1**, that was directly reduced to the saturated alcohol.

Here we wish to report that using SiO_2-TiO_2 or SiO_2-ZrO_2 as the catalyst support, an unprecedented reaction takes place leading to moderate to good yields of bicyclic ethers.





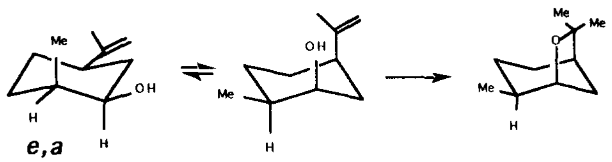
Formation of these ethers is worth noting from both a mechanistic and a synthetic point of view. From the mechanistic point of view, this reaction accounts for the presence of two different sites on the catalyst surface: an hydrogenation site consisting of reduced Cu particles that chemoselectively reduces the conjugate enone group to the corresponding alcohol, and an acidic site which activates the olefinic bond as a carbonium ion, thus allowing the nucleophilic addition of the hydroxy group.

Results obtained in the presence of our catalysts are summed up in Table 1.

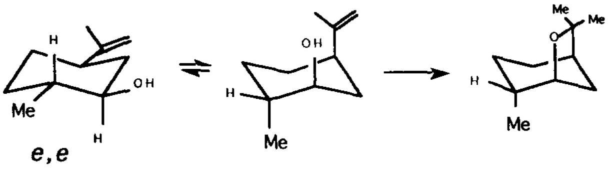
The reaction is very slow under 1 atm of H_2, but can be conveniently speeded up by using a low hydrogen pressure and the products can be easily recovered avoiding all the work up procedures required by a conventional acid catalyzed reaction.

An interesting feature is the high stereoselectivity observed in the synthesis of dihydropinol **2** (2,6,6-trimethyl-7-oxabicyclo[3,2,1]octane), the *cis* isomer being formed with up to 96% selectivity. If we look at the four epimers that can form during hydrogenation of **1**, we can see that only two of them can assume a conformation suitable for the cyclization reaction, namely the two with the hydroxy group in equatorial position.

In particular, the *e,a* one would give the *cis* product, whereas the *e,e* would give the *trans*.



2a *cis*



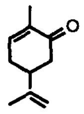
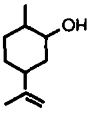
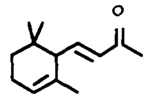
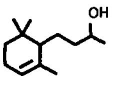
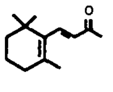
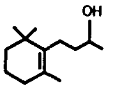
2b *trans*

Our previous work on the hydrogenation of **1** showed that the *e,a* alcohol is the main isomer formed in the presence of both Cu/SiO_2[2] and Cu/Al_2O_3.[3] Therefore we can suggest that the stereochemistry observed depends on the presence of copper in the reduction step. According to this hypothesis, reaction of a commercial mixture of dihydrocarveols containing only a minor amount of the suitable isomers (10% of the *e,a* isomer, 13% *e,e*, 66% *a,e*, 11% *a,a*) in the presence of our catalyst, gave a low yield in dihydropinol with a very low cis/trans ratio (entry 7), whereas a mixture obtained by hydrogenation of **1** in the presence of Cu/SiO_2 (41% of the *e,a* epimer, 19% *e,e*, 34 % *a,e*, 6% *a,a*) gave good yield and good stereoselectivity (entry 5,6), the byproduct being a mixture of unreacted isomeric alcohols that can be recycled.

Reaction of α and β-ionone gave mixtures of tetrahydroedulan (2-oxabicyclo[4.4.0]decane) isomers **5a-d**. However, the reaction can be easily stopped at the monohydrogenated ketone stage by working at 1 atm of H_2, or at the unsaturated alcohol stage under conditions that suppress the acidic reaction, e.g. by using 2-propanol as a solvent.

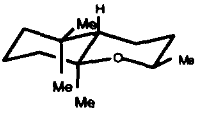
α-Ionone gave mixture of cis and trans isomers, but allowing α-dihydroionols to react in a separated step, a significant increase in *cis* products **5c** and **5d** was obtained (entry 10). On the other hand, the same

Table 1.Synthesis of bicyclic ethers in the presence of 8% copper catalysts

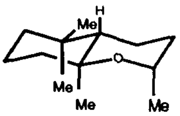
Substrate	Entry	conditions	t (h)	conv.	sel (%)	Prod. distribution (%)			
						2a	2b		
 **1**	1	Cu/SiTi, *a*	23	100	61	84	16		
	2	", *b*	7	100	51	96	4		
	3	Cu/SiZr, *c*	5	100	46	90	10		
	4	", *b*	3	100	55	91	9		
 **3** *e*	5	Cu/SiTi, *d*	6	56	42	91	9		
	6	Cu/SiZr, *a*	2	82	66	75	25		
3 *f*	7	Cu/SiTi, *a*	6	35	74	60	40		
						5a	5b	5c	5d
 **4**	8	Cu/SiTi, *b*	8	100	43	12	26	34	28
	9	Cu/SiZr, *c*	4	100	55	14	27	31	29
 **6**	10	Cu/SiTi, *d*	6	76	61	11	6	38	45
 **7**	11	Cu/SiTi, *b*	14	100	55	53	16	19	12
	12	", *c*	24	87	69	57	18	14	11
	13	Cu/SiZr, *c*	4	100	61	61	16	14	9
 **8**	14	Cu/SiTi, *d*	11	95	80	59	14	19	8

conv. = % starting material consumed; sel. = amount of ethers/conv
a = n-heptane, 90°C, 1 atm H_2; *b* =toluene, 110°C, 6 atm H_2; *c* = n-heptane, 90°C, 6 atm H_2;
d= toluene, 110°C, 1 atm H_2; *e* = 41% *e,a*; 19% *e,e*; 34% *a,e*; 6% *a,a*.
f = 10% *e,a*; 13% *e,e*; 66% *a,e*; 11% *a,a*.

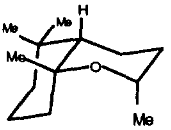
stereochemistry, favouring the two *trans* isomers **5a** and **5b**, was obtained starting from both β-ionone (entry 11 and 13) and β-dihydroionol (entry 14).



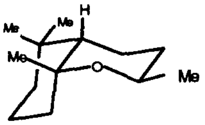
5 a



5 b



5 c



5 d

Catalyst preparation: The catalysts were prepared and reduced before the reaction as already reported[2] for Cu/SiO_2 , but using two mixed oxides obtained from Grace Davison GmbH, In der Hollerhecke 1, D-67547 Worms (Germany), namely SiO_2-TiO_2 0.3% TiO_2, S_{BET} 330 m^2/g, PV 1.90 ml/g, SiO_2-ZrO_2, 4.7% ZrO_2, S_{BET} 320 m^2/g, PV 1.60 ml/g.

Experimental conditions: The reduced catalyst (0,3 g) and the substrates (2 mmoles), dissolved in toluene or n-heptane (14 ml), were allowed to react under H_2 in a stainless steel autoclave under the conditions listed in the Table. GC analysis were carried out on a 60 m polyethylene glycol (Supelcowax 10) or a 30 m poly (80%-biscyanopropyl-20%cyanopropylphenylsiloxane) capillary column. After completion the reaction mixture was separated by flash chromatography and the products characterized through comparison of their IR, ^{1}H NMR and ^{13}C NMR, with those reported in the literature.[4-6] The stereoisomer distribution was determined by GC and by 500 MHz ^{1}H NMR.

α-dihydroionol **6** and β-dihydroionol **8** were obtained through hydrogenation of **4** and **7** respectively in the presence of Cu/SiTi, in 2-propanol, at 110°C and under 6 atm of H_2 (82% yield).

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   Significative resonances are reported hereafter. Although the chemical shifts are in agreement with those reported in the paper, the J values strongly suggest that the isomer with a ddq at 3.63 ppm should be assigned structure **5c**.^{1}H NMR ($CDCl_3$, 500 MHz) **5a** : 0.74 (s/3H); 0.86 (s/3H); 1.09 (d/3H, 6.1 Hz); 1.22 (s/3H); 3.74 (ddq/1H, J=2.6, 10.0, 6.1 Hz). **5b**: 0.79 (s/3H); 0.87 (s/3H); 1.12 (d/3H, 6.3 Hz); 1.20 (s/3H); 3.99 (ddq, J=3.8, 8.4, 6.3 Hz). **5c** : 0.85 (s/3H); 1.08 (d/3H, J=6.1 Hz); 1.09 (s/3H); 1.35 (s/3H); 3.63 (ddq, J=2.1, 5.9, 6.1 Hz). **5d**: 0.89 (s/3H); 1.06 (s/3H); 1.09 (d/3H, J=6.0 Hz); 1.22 (s/3H); 3.86 (ddq, J=3.7, 11.5, 6.0 Hz).

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