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COPPER-CATALYSED REACTIONS OF GRIGNARD REAGENTS WITH EPOXIDES AND OXETANE.

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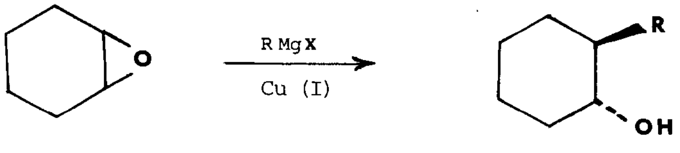
ABSTRACT :

The copper-catalysed ring opening of epoxides and oxetane by Grignard reagents proceeds in good yield under mild conditions.

The nucleophilic ring opening of epoxides by organometallic reagents is a frequently used method for the generation of new carbon-carbon σ bonds [1]. The utilisation of Grignard reagents is a well established route [2,3] ; however it has been limited in scope due to competing reactions arising from either the Lewis acidity or the basicity of the organometallic reagent. These different mechanistic pathways have been investigated [4] .
We now report the efficient copper-catalysed [5] reaction of Grignard reagents with epoxides which proceeds in high yield under very mild conditions. Thus, when cyclohexene oxide (1 equiv.) was treated with phenylmagnesium chloride (1.5 equiv.) and copper iodide (0.15 equiv.) in tetrahydrofuran at 0° for 2 hr, trans-2-phenyl-cyclohexanol [6] was obtained in 82% yield. Without the copper salt, in the same conditions (2 hr at 0°), less than 3% of alcohol 2a was formed along with side products and unchanged starting material (40%).
Several representative Grignard reagents listed in table 1 led to similar results.

Benzylmagnesium chloride was found to be more reactive and copper catalysis was not required for the efficient ring opening of the epoxides ; thus, when treated with cyclohexene oxide in tetrahydrofuran at 0° without copper salt, this reagent gave, within 2 hr, pure trans-2-benzyl-cyclohexanol in 90% yield.



1 2

Table 1 : Reaction of Grignard reagents (1.5 equiv.) with cyclohexene oxide (1 equiv.) in THF after 2 hr ar 0° :

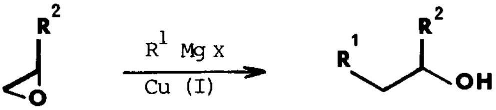
PRODUCT	R	X	Yield [a] (%) with 10 % Cu I	Yield [a] (%) without catalyst
2a	C_6H_5	Cl	82[b]	3
2b	$n\text{-}C_4H_9$	Cl	58[c]	6
2c	$CH_3\text{-}\underset{\vert}{C}\text{=}CH_2$	Br	88	40[d]
2d	$(CH_3)_2C\text{=}CH\text{-}CH_2$	Cl	86[e,f]	86[g]
2e	$C_6H_5CH_2$	Cl	40	86[h]

[a] yield of distilled product calculated from cyclohexene oxide. [b] Containing 6% of *trans*-2-iodo-cyclohexanol. [c] 10% of cyclohexanone were formed : This side product was also observed with lithium cuprates, see ref.7. [d] Without copper salt, after 6 hr at 0° and 1 hr at room temperature, alcohol **2c** was obtained in 80% yield. [e] This reaction was carried out at - 30° [8b]. [f] By using 1.5 equiv. of copper iodide, predominant formation of *trans*-2-iodo-cyclohexanol was observed. However, by using 3 equiv. of copper bromide, and 3 equiv. of Grignard reagent, 67% of alcohol **2d** were obtained. [g] see ref. 8b. [h] see ref. 9.

Monosubstituted epoxides and ethylene oxide are more reactive than disubstituted epoxides towards Grignard reagents and are less dependent upon copper catalysis. Thus, when propylene oxide (1 equiv.) was treated with butyl magnesium chloride (1.5 equiv.) and copper bromide (0.15 equiv.) in tetrahydrofuran for 2 hr at 0°, it gave pure heptan-2-ol in 93% yield. Without catalyst, in the same conditions, the yield was only 26% because of incomplete reaction ; however after 8 hr at room temperature, alcohol **4c** was formed in 86% yield.

The less strained cyclic ether, oxetane **5**, has lower reactivity than epoxides[11,12,13]. The ring cleavage of this compound by Grignard reagents has been reported by refluxing in benzene for several hours [11]. However, when treated at room temperature for 20 hr in tetrahydrofuran with 10% of copper iodide, it gave the alcohols **6** in acceptable yields.

These catalytic processes represent a useful procedure for the ring opening of epoxides and oxetane by Grignard reagents.

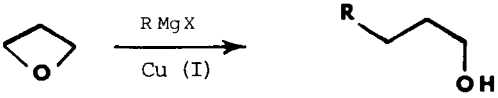


3 **4**

Table 2 : Reaction of Grignard reagents (1.5 equiv.) with epoxides 3 (1 equiv.) in tetrahydrofuran after 2 hr at 0° :

PRODUCT	R^1	R^2	X	Yield[a] (%) with 10% CuBr	Yield[a] (%) without catalyst
4a	C_6H_5	CH_3	Cl	95	80
4b	C_6H_5	H	Cl	81[b]	75[c]
4c	$n\text{-}C_4H_9$	CH_3	Cl	93	26[e]
4d	$n\text{-}C_4H_9$	H	Cl	88[b]	55[d]
4e	$CH_3\text{-}\underset{\vert}{C}\text{=}CH_2$	CH_3	Br	90	90
4f	$C_6H_5CH_2$	CH_3	Cl	91	95

[a] Yield of distilled product calculated from epoxide 3. [b] 1 equiv. of Grignard reagent was used. [c] see ref. 10. [d] see ref. 3. [e] Without copper salt, after 1 hr at 0° and 8 hr at room temperature, alcohol 4c was obtained in 86% yield.



5 **6**

Table 3 : Reaction of Grignard reagents (1 equiv.) with oxetane (3 equiv.) in the presence of 10% of copper iodide [a] :

PRODUCT	R	X	Solvent	Yield [b] (%)
6a	$n\text{-}C_4H_9$	Cl	ether	75[c]
6b	C_6H_5	Br	THF	52
6c	$CH_2\text{=}CH\text{-}CH_2$	Br	ether	50
6d	$(CH_3)_2C\text{=}CH\text{-}CH_2$[d]	Cl	THF	50[e,f]

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[a] The addition of the reagent to the oxide was carried out at -30° and the reaction mixture was allowed to warm to room temperature and maintained at +20° for 20 hr unless otherwise noted. [b] Distilled yield based on Grignard reagent. Identity was confirmed by comparison with an authentic sample. [c] Without copper iodide, after 90 hr at 0°, 10% of n-heptanol were formed. [d] See ref. 8. [e] This reaction was carried out at 0° for 20 hr. [f] 3% of 4-4-dimethyl-5-hexenol were also formed. Without copper salt, after 12 hr at 0°, a mixture (15:85) of 6d and 4-4-dimethyl-5-hexenol was obtained in 75% yield.

TYPICAL PROCEDURE FOR THE RING OPENING OF EPOXIDES.

Trans-2-phenyl-cyclohexanol : To 430 mg (2.3 mmol) of copper iodide [14] in anhydrous THF (10 ml), 23 mmol (2.25N in THF) of phenylmagnesium chloride were added dropwise at -30°. After 5 mm at -30°, 1.47g (15 mmol) of cyclohexene oxide were added. The mixture was allowed to warm to 0° and maintained at this temperature for 2 hr. Work-up in the usual manner and distillation gave 2,16 g (82%) of *trans*-2-phenyl-cyclohexanol **2a**, b.p. 102-103°/0.5 mm ; m.p. 57-58° (from pentane)[6].

TYPICAL PROCEDURE FOR THE RING OPENING OF OXETANE **5**. To 164 mg (0.862 mmol) of copper iodide [14] and 2 g (34mmol) of oxetane in anhydrous ether (15 ml), 8.62 mmol (1.98N in ether) of *n*-butylmagnesium chloride were added dropwise at -30°. The reaction mixture was allowed to warm to room temperature and stirring was maintained for 20 hr. Then, the mixture was hydrolysed with saturated ammonium chloride, extracted with ether and the combined extracts dried and evaporated. Distillation gave 750 mg (75%) of *n*-heptanol.

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