Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7349-7352, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10009-0

Magnesium Promoted Cyclopropanation Reactions of Allylic Alcohols

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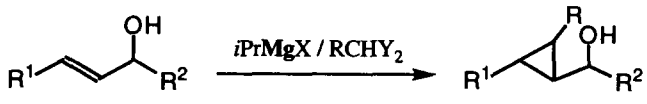
Abstract: Treatment of allylic alcohols **1** with various magnesium reagents in the presence of alkyl dihalides affords the corresponding cyclopropyl alcohols **2**. Reactions occur under mild conditions, and excellent diastereoselectivities have been achieved.

Key Words: Allylic Alcohols, Carbenoids, Cyclopropanation, Grignard Reagents, Magnesium

Cyclopropanation of olefins is one of the most important methods in the repertoire of today's organic synthesis.[2,3] Since the pioneering work of *Simmons* and *Smith*[4] in 1958 several modifications using carbenoid species to convert alkenes into the corresponding cyclopropanes have been developed.[2] Most of them involve zinc reagents,[5] and by using those in auxiliary-based[6] or reagent-controlled transformations[7] high stereoselectivities have been achieved. Recently, the first catalytic enantioselective cyclopropanations of this type have been reported.[8] Besides zinc, samarium and aluminium have been used in methylene transfer reactions.[9] We now developed a new method employing simple Grignard reagents. With this convenient procedure allylic alcohols are easily transferred to the corresponding cyclopropane derivatives. The reaction is highly stereoselective, and even substituted methylene groups can add to the olefinic precursor.[10]

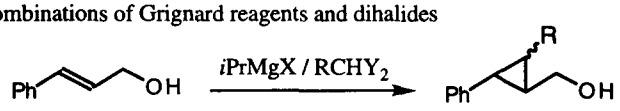


1 **2**

X = I, Br, Cl, *i*Pr;
Y = Br, I

We started our investigation by testing the capability of various combinations of magnesium reagents and dihalides to perform cyclopropanations of cinnamic alcohol (**1a**). As summarized in Table 1, the best result in these early studies was achieved with isopropyl magnesium iodide and diiodomethane. Interestingly, even a longer-chain 1,1-diiodo alkane reacted (entry 7) affording, though in low yield, the corresponding trisubstituted cyclopropane alcohol **2b**.[11]

Table 1: Magnesium promoted cyclopropanation of cinnamic alcohol with various combinations of Grignard reagents and dihalides



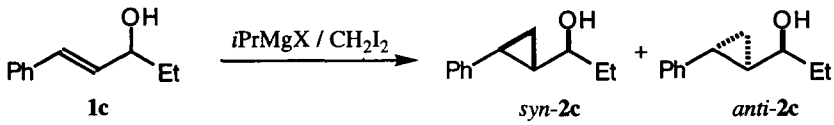
1a **2a**: R = H; **2b**: R = *n*Bu

Entry	Grignard reagent	Dihalide	R	Product	Yield [%]
1	*i*PrMgCl	CH_2I_2	H	**2a**	35 [a]
2	*i*PrMgBr	CH_2I_2	H	**2a**	30 [b]
3	*i*PrMgI	CH_2I_2	H	**2a**	47 [b]
4	$Mg(iPr)_2$	CH_2I_2	H	**2a**	38 [b]
5	*i*PrMgCl	CH_2Cl_2	H	**2a**	---
6	*i*PrMgCl	CH_2Br_2	H	**2a**	19 [a]
7	*i*PrMgCl	$C_5H_{10}I_2$	C_4H_9	**2b**	10 [a]

[a] Yield after 60 h. [b] Conversion after 48 h.

Further studies revealed that an excess of both magnesium reagent and dihalide was required for high conversion of the starting material. Thus, the optimized reaction protocol involves the successive addition of 4 equiv. of a Grignard reagent in THF or ether and 3 equiv. of the alkyl dihalide to a solution of the allylic alcohol in anhydrous CH_2Cl_2 (10 ml/mmol) at -70 °C. The resulting mixture is then stirred at this temperature for 48 h to 60 h followed by quenching with a saturated aqueous solution of NH_4Cl. Conversion and diastereoselectivity were determined on crude reaction mixtures by capillary gas chromatography. Simple aqueous workup followed by flash chromatography afforded pure product.

The diastereoselectivity of the cyclopropanation reaction using magnesium reagents was studied using *trans*-1-phenyl-1-penten-3-ol (**1c**) as substrate and diiodomethane as methylene source.



1c *syn*-**2c** *anti*-**2c**

In this case, the best yield (78%) of **2c** and the highest *syn/anti*-ratio (24 : 1) were obtained with the Grignard reagent prepared from isopropyl chloride. Other alkyl magnesium halides and diisopropyl magnesium gave less satisfying results (Table 2). Presumably, a smaller size of the counter ion of the Grignard reagent allows the formation of a more compact transition state resulting in higher reactivity and stereoselectivity.

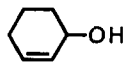
Table 2: Magnesium promoted cyclopropanation of *trans*-1-phenyl-1-penten-3-ol (**1c**)

Entry	Grignard reagent	Yield of **2c** [%] [a]	*syn*-**2c** : *anti*-**2c** [b]
1	*i*PrMgCl	78	24 : 1
2	*i*PrMgBr	29	10 : 1
3	*i*PrMgI	4	5 : 1
4	$Mg(iPr)_2$	4	3 : 1

[a] Conversion after 60 h. [b] Determined by GC of the corresponding benzoates.

In order to study the scope of this cyclopropanation, reactions of various secondary allylic alcohols were investigated. As summarized in Table 3 very high diastereoselectivities (> 400 : 1) in favor of the *syn*-isomer were obtained when substrates with bulky substituents at the hydroxyl-bearing carbon were used (entries 3 and 4). 2-Cyclohexenol (**1g**) afforded the *syn*-diastereomer exclusively (entry 5).

Table 3: Magnesium promoted cyclopropanation of various allyl alcohols

Entry	Substrate	Yield [%] [a]	*syn*- : *anti*-Product [b]
1	**1d** (R^1 = Ph, R^2 = Me)	50	5 : 1
2	**1c** (R^1 = Ph, R^2 = Et)	73	24 : 1
3	**1e** (R^1 = Ph, R^2 = *i*Pr)	82	> 400 : 1
4	**1f** (R^1 = Ph, R^2 = *t*Bu)	78	> 400 : 1
5	 **1g**	79	*syn* only

[a] Yield of *syn*-product. [b] Determined by GC of the corresponding benzoates.

In conclusion, we have demonstrated that simple magnesium reagents are capable to promote cyclopropanation reactions of allylic alcohols. With appropriate substrates the reaction proceeds with excellent diastereoselectivities. Currently, we are investigating the possibility of using chiral ligands to promote asymmetric transformations of this kind.

Acknowledgment: This research has been supported by the *Deutsche Forschungsgemeinschaft* (SFB 260, Graduiertenkolleg) and the *Fonds der Chemischen Industrie.*

References and Notes

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11. NMR data of 1-hydroxymethyl-2-phenyl-3-butylcyclopropane (**2b**, major diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ = 0.96-1.03 (m, J = 9.0 Hz, 1H), 0.76-1.60 (m, 8H), 1.39-1.47 (m, J = 6.8 Hz, J = 5.1 Hz, 1H), 2.02 (dd, J = 9.0 Hz, J = 5.3 Hz, 1H), 3.64 (d, J = 6.8 Hz, 2H), 7.14-7.92 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ = 13.9, 22.3, 24.9, 26.3, 26.7, 27.3, 31.6, 66.8, 125.7, 127.9, 128.9, 138.5 ppm.

(*Received in Germany* 14 *July* 1997; *accepted* 28 *August* 1997)