

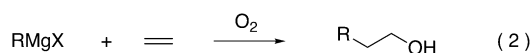
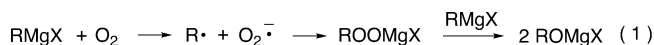
Air-Assisted Addition of Grignard Reagents to Olefins. A Simple Protocol for a Three-Component Coupling Process Yielding Alcohols

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Oxidation of Grignard reagents with O₂ is well-known to yield alcohols via a radical mechanism (eq 1).¹ However, to our best knowledge, application of the intermediate radicals (R•) has not been fully investigated from the synthetic point of view.^{1a,2,3} Grignard reagents are generally reluctant to add to olefins, and methods to execute this type of reaction are still limited.^{4,5} Herein we report a new and simple entry to Grignard addition to olefins, which takes advantage of the radical species generated by the aerial oxidation of Grignard reagents and enables a one-pot, three-component coupling process of a Grignard reagent, olefin, and O₂ (air), directly yielding alcohols according to eq 2.



The feasibility of intermolecular addition of various Grignard reagents **1–8** according to eq 2 was first evaluated with α -methylstyrene (**9**) (eq 3, Table 1). An attempted addition of butyl or *i*-propyl Grignard reagents to this olefin failed (entries 1 and 2). This is in accord with a precedent that exposure of 5-hexenyl Grignard reagent to O₂ gave cyclopentylmethanol as a *minor* component, showing that the addition of the transient alkyl radical to olefin is not a preferable path even in an intramolecular manner.^{1a} However, gratifyingly, we found that certain Grignard reagents, such as those having *tertiary*-alkyl, alkenyl, and aryl groups (**3–6**), nicely undergo the intermolecular addition to **9** followed by the oxygenation with O₂ to yield alcohols **12–15** (entries 3–6). In addition, silylmethyl Grignard reagent **7** or **8** is an exceptional *primary*-alkyl reagent that participates in the present reaction (entries 7 and 8).^{6–8} As far as the solvents are concerned, both ether and THF, common solvents for the preparation of Grignard reagents, are acceptable for this process (Table 1).^{9,10}

That the above reaction is actually assisted by O₂ and does not involve the carbomagnesiation/oxidation sequence has been evi-

Table 1. O₂(Air)-Assisted Intermolecular Addition of Grignard Reagents

	RMgX				
	(1–8) (3 equiv)	(9) (1 equiv)	$\xrightarrow[\text{overnight}]{\text{O}_2 \text{ (air)}}$		(10–17)
entry	RMgX	solvent	product	yield (%)	
1	BuMgBr	(1)	Et ₂ O	10	<10
2	<i>i</i> -PrMgCl	(2)	Et ₂ O	11	<10
3	<i>t</i> -BuMgCl	(3)	Et ₂ O	12	74
4	Me ₂ C=C(H)MgBr	(4)	THF	13	72
5	H ₂ C=C(Me)MgBr	(5)	THF	14	70
6	PhMgBr	(6)	THF	15	75
7	Me ₃ SiCH ₂ MgCl	(7)	Et ₂ O	16	72–90 ^a
8	Me ₂ PhSiCH ₂ MgCl	(8)	Et ₂ O	17	74 ^b

^a Range of yields in different scales. See Supporting Information.
^b Me₂PhSiCH₂OH (2.0 equiv) was also produced.

Scheme 1. Confirmation of the O₂-Assisted Mechanism

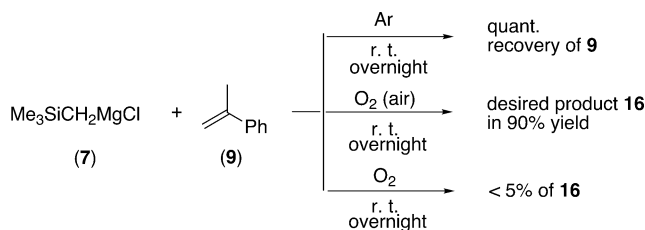


Table 2. Air-Assisted Addition of Grignard Reagents to Various Olefins^a

	R ¹ MgX				
	(5), (7)	(18–24)	$\xrightarrow[\text{overnight}]{\text{O}_2 \text{ (air)}}$		(25–31)
Entry	R ¹ MgX ^b	Olefin	Product	Yield (%) ^c	
1	7	(18)	70:30 HO-CH ₂ -CH ₂ -SiMe ₃ (25)	75	
2	7^d	(19)	86:14 HO-CH ₂ -CH ₂ -SiMe ₃ (26)	68	
3	7	(20)	HO-CH ₂ -CH ₂ -SiMe ₃ (27)	80	
4	7	(21)	HO-CH ₂ -CH ₂ -SiMe ₃ + HO-CH ₂ -CH ₂ -SiMe ₃ (28) 1:1	65	
5	7	(22)	HO-CH ₂ -CH ₂ -SiMe ₃ + HO-CH ₂ -CH ₂ -SiMe ₃ (29) 1:1	80	
6	7	(23)	HO-CH ₂ -CH ₂ -SiMe ₃ + HO-CH ₂ -CH ₂ -SiMe ₃ (30) 1:1	76	
7	5	(24)	HO-CH ₂ -CH ₂ -SiMe ₃ (single isomer) (31)	68	

^a For reaction conditions, see eq 3. ^b Me₃SiCH₂MgCl (**7**) in Et₂O or H₂C=C(Me)MgBr (**5**) in THF. ^c Isolated yields. ^d Four equivalents of **7** was used.

denced by the following experiments (Scheme 1). When a mixture of Grignard reagent **7** and olefin **9** was stirred under argon with rigorous exclusion of O₂, nearly complete recovery of **9** and the absence of a coupling product resulting from carbomagnesiation were observed.¹¹ To the contrary, it is interesting to note that a similar reaction under a (pure) O₂ atmosphere did not give the desired product **16** due perhaps to much accelerated oxygenation of the Grignard reagent itself.¹²

Table 3. Regioselective Addition of Grignard Reagents to Enynes^a

$\text{R}^1\text{MgX} + \text{R}^2\text{C}\equiv\text{C}-\text{CH}=\text{CH}-\text{R}^3 \xrightarrow[\text{overnight}]{\text{O}_2 (\text{air}), \text{r. t.}} \text{R}^2\text{C}\equiv\text{C}-\text{CH}(\text{OH})-\text{CH}(\text{R}^1)-\text{R}^3$					
<div style="display: flex; justify-content: space-around; align-items: center;"> <div>(5-8)</div> <div>(32-34)</div> <div></div> <div>(35-40)</div> </div>					
entry	R ¹ MgX	Enyne		product	yield (%) ^b
		R ²	R ³		
1	PhMe ₂ SiCH ₂ MgCl (8)	C ₁₀ H ₂₁ (32)	H (35)	35	71
2	Me ₃ SiCH ₂ MgCl (7)	" (33)	Me (36)	36	70
3	PhMe ₂ SiCH ₂ MgCl (8)	" (33)	" (37)	37	76
4	H ₂ C=C(Me)MgBr (5)	" (33)	" (38)	38	55
5	PhMgBr (6)	" (33)	" (39)	39	48
6	PhMe ₂ SiCH ₂ MgCl (8)	SiMe ₃ (34)	C ₉ H ₁₉ (40)	40	88

^a Reaction conditions are the same as those of eq 3. ^b Isolated yields.**Table 4.** Dual Grignard System Decreasing the Stoichiometry of Precious Grignard Reagent

$\text{Me}_3\text{SiCH}_2\text{MgCl} + \text{t-Bu-C}_6\text{H}_4\text{-CH=CH}_2 \xrightarrow[\text{O}_2 (\text{air})]{\text{BuMgBr (1)}} \text{t-Bu-C}_6\text{H}_4\text{-CH(OH)-CH}_2\text{-SiMe}_3$			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div>(7)</div> <div>(41) (1 equiv)</div> <div></div> <div>(42)</div> </div>			
entry	7 (equiv)	1 (equiv)	yield of 42 (%)
1	3	0	78
2	1.2	0	32
3	1.2	1.2	64
4	1.5	0.8	65

This reaction shows reasonable generality not only to styrenes **18–20** but also to conjugated dienes **21–24** (Table 2). Good diastereoselectivity was observed in entry 2, where the protection of the free hydroxy group of **19** is not necessary. As this reaction does not involve an unstable α -furfuryl carbanion¹³ arising from carbomagnesiation, furfuryl alcohol **27** was obtained without difficulty (entry 3). In all cases, the first radical addition to olefins took place at the unsubstituted methylene moiety in a highly regioselective manner. Although the successive oxygenation of the resulting pseudo-symmetrical allyl radicals gave a regioisomeric mixture of allyl alcohols (entries 4–6), a suitably substituted diene **24** nicely afforded a single isomer **31** (entry 7).¹⁴ A more dependable regiochemical control of both Grignard addition and oxygenation was achieved in the reaction of conjugated enynes, such as **32–34**,¹⁵ giving solely propargyl alcohols **35–40** unaccompanied by isomeric unsaturated ketones and allenyl alcohol (Table 3).¹⁶

Throughout the above transformations, excess use of Grignard reagent is mandatory because at least 1 equiv of the reagent was consumed for the reduction of the resultant hydroperoxide, yielding nonhomologated alcohols, as mentioned in footnote b to Table 1. To save the precious Grignard reagent, we tried the reaction in the presence of a second Grignard reagent that does not add to olefin, but solely decomposes the intermediate hydroperoxide. To our satisfaction, BuMgBr works quite well as the second Grignard reagent, and, in its presence, a slight excess Grignard reagent **7** and olefin **41** now afforded the product **42** in good yield (entry 3 or 4 as compared to entry 1, Table 4), close to that of the original reaction conditions (entry 1).

In conclusion, the above reaction provides a very simple three-component coupling process, free of additional or toxic reagents, such as transition metal salts or organotin and related reagents, to yield alcohols.

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Supporting Information Available: Experimental procedures, structural determinations, and spectroscopic properties of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) For comparison, yields of **16** obtained with Me₃SiCH₂Mg under the conditions of eq 3 are as follows: M = Li, 42%; MgCl, 90%; ZnCl 13%. Thus, the Grignard reagent gave the most satisfactory result.
- (9) Although THF often blocks a desired radical reaction via its hydrogen radical abstraction, this was not observed.
- (10) *Caution: Although, in these reactions, hydroperoxide was not produced in an isolable amount in our hands, care must be taken in the formation of peroxides particularly in a large-scale preparation. For more details, see Supporting Information.*
- (11) The same recovery of olefinic substrates under pure argon was further confirmed in other reactions of entry 6 of Table 2, and entries 2, 4, and 5 of Table 3.
- (12) This means that, although we used dry air throughout this study owing to its convenience and economy, careful optimization of the partial pressure of O₂ may lead to higher product yields with less equivalents of Grignard reagent.
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- (16) A nonconjugated olefin, such as 1-octene, did not participate in the present radical addition.

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