

Stereochemical Study of the Allylation of Aldehydes with Allyl Halides in Cosolvent/Water(Salt)/Zn and in Cosolvent/Water(Salt)/Zn/Haloorganotin Media

Daniele Marton, Diego Stivanello, and Giuseppe Tagliavini*

Dipartimento di Chimica Inorganica, Metallorganica e Analitica, Università di Padova, Via Marzolo, 1, I 35131 Padova, Italy

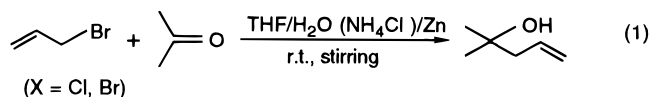
Received August 25, 1995[®]

The stereochemical course of the allylation and propargylation of several aldehydes with crotyl and propargyl halides using zinc powder as the condensing agent in cosolvent/water(salt) media have been extensively studied. Radical ions of well-defined geometry such as $[\text{CH}_2=\text{CHCH}(\text{CH}_3)\text{Br}]^{\cdot-}$ are thought to be formed through an electron-transfer process, which seems to be accelerated by the high interfacial energy developed by the water. These radicals are trapped by the aldehyde molecules to form isomeric mixtures of *threo*/*erythro*- β -methylhomoallylic alcohols or α -allenic/ β -acetylenic alcohols. The stereochemistry seems to be determined by the structure of the radical anions adsorbed on the zinc particles and is independent of the geometry of the organic halides, the cosolvents, or the salts. Reactions performed in the presence of Bu_3SnCl show no discrimination between the coupling reactions of the allyl bromide with aldehydes and with Bu_3SnCl , both homoallylic alcohols and allyltributylstannanes being formed. In contrast, in the presence of Bu_2SnCl_2 only β -methylhomoallylic alcohols are formed, this being a function of the differential allylstannation of aldehydes and crotyldibutyltin halides, which are intermediate products of the zinc-mediated process. The zinc-mediated method gives satisfactory results with acetals if workup is made under the catalytic mediation of Bu_2SnCl_2 .

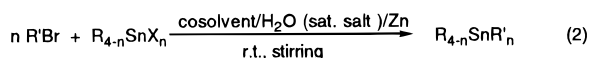
Introduction

Of special interest in recent years has been the use of water—either alone or with cosolvent—as a medium for reactions with organic or organometallic reagents.^{1–3} In the organometallic field, particular attention has been paid to the use of allyl- and allyllike-tin halides, as well as BuSnCl_3 , as reactants in water for C–C^{4–7} and C–O–C^{8–10} bond-forming reactions under homogeneous or heterogeneous conditions. Also, silicon and tin allyl derivatives have been used for aminoethanodesilylation–cyclization^{11,12} and aminomethanodestannylation¹³ processes, with water.

A very versatile procedure based on the mediation of zinc powder^{14–16} (eq 1) has been adopted for the preparation of homoallylic alcohols.



The same procedure has been recently employed to prepare mixed allylstannanes^{17,18} by coupling reactions of allyl or allyllike bromides with $\text{R}_{4-n}\text{SnX}_n$ substrates (eq 2).



(R' = allyl or allyllike group, propargyl; R = Me, Et, Pr, Bu, and Ph; X = Cl, I, OH; n = 1 and 2; cosolvent = cyclohexane, toluene, THF, 2-propanol, acetonitrile, pyridine; salt = NaCl, NH_4Cl , LiClO_4 , $\text{NH}=\text{C}(\text{NH}_2)\text{HCl}$)

The zinc-mediated method has also been applied to the preparation of distannanes¹⁸ and mixed benzylstannanes.¹⁹

A close correlation exists between the reactions represented in eqs 1 and 2. In both cases, intermediate radical ions of the type $[\text{CH}_2=\text{CHCH}_2\text{Br}]^{\cdot-} \text{Zn}^+$ are thought to be trapped by electrophilic species, aldehydes in eq 1 and $\text{R}_{4-n}\text{SnX}_n$ in eq 2. A further similarity is the observed high regioselectivity; aldehydes and organotin derivatives react at the more substituted carbon of the allyl halides, giving rise to β -methylhomoallylic alcohols¹⁶ and (α -methylallyl)tin derivatives²⁰ respectively, when crotyl halides are used. With regard to the stereochemical outcomes of these reactions, those of eq 2 have been

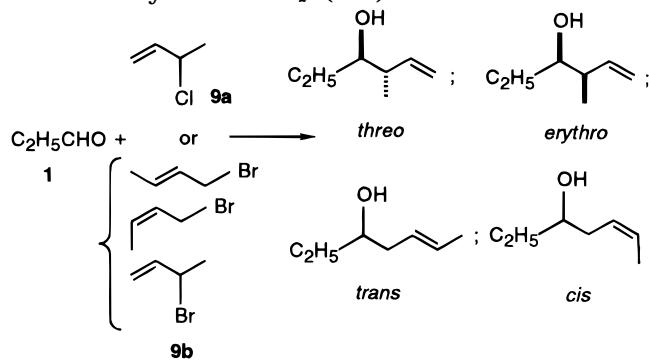
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(20) Bu_3SnCl reacts with an isomeric mixture of $(\text{C}_4\text{H}_7)\text{Br}$ (C_4H_7 stands for α -methylallyl (15%) and *trans*- (76%) and *cis*-crotyl (9%), in cyclohexane/ H_2O (NH_4Cl)/Zn medium to form selectively $\text{Bu}_3\text{SnCH}(\text{CH}_3)\text{CH}=\text{CH}_2$ (see ref 18).

Table 1. Stereochemical Course of the Reactions between Propionaldehyde and Allyl Halides in Cyclohexane/H₂O(Salt)/Zn Medium^a

entry no.	salt	allyl halide	isolated product yield, %	isomeric composition, %		
				<i>threo</i>	<i>erythro</i>	(<i>trans</i> + <i>cis</i>)
1	NH ₄ Cl	9a	40	53	47	
2	NH ₄ Cl	9b	39	52	48	
3	NaCl	9a	67	53	44	3
4	NaCl	9a	81	51	46	3
5	NaCl ^b	9a	76	51	45	4

^a Reactions conditions: 0.15 mol of **1** and 0.30 mol of **9a** or **9b** in entries 1–3; 0.30 mol of **1** and 0.15 mol of **9a** or **9b** in entries 4 and 5; 25 mL of cyclohexane; 50 mL of water (saturated with salt); 0.30 mol of Zn powder (325 mesh). ^b NaCl saturated aqueous solution with 1 mL of HClO₄ 70%, pH = 0.63.

more extensively examined than those of eq 1. Therefore, we have studied under different experimental conditions the coupling of the aldehydes RCHO [R = C₂H₅ (**1**), (CH₃)₂CH (**2**), (CH₃)₃C (**3**), *cyclo*-C₆H₁₁ (**4**), C₆H₅ (**5**), CH₂=CH (**6**), CH₃CH=CH (**7**), and CH₃(CH₂)₂CH=CH (**8**)] with CH₂=CHCH(CH₃)Cl (**9a**) or (C₄H₇)Br (**9b**)²¹ and reactions of aldehyde **2** and propargyl bromide (**10**). Also, the effect of various cosolvents (THF, cyclohexane, acetonitrile) or salts in the aqueous phase (NH₄Cl, NH=C(NH₂)·HCl, NaCl, LiClO₄, ZnCl₂) has been studied.

Mixtures of (CH₃)₂CHCHO and Bu₂SnCl₂ have been allowed to react with (C₄H₇)Br and zinc in cyclohexane/H₂O (salt) media. Thus, we have verified how the stereochemical course of the coupling reaction leading to β-methylhomoallylic alcohols *via* eq 1 is influenced by the competitive allylstannation of the aldehyde^{6,7,22} on account of the crotyldibutyltin chloride formed *via* eq 2. Following this line, we also have found that the acetal CH₃CH(OCH₃)₂ (**11**) reacts with **9b** in the presence of catalytic amounts of Bu₂SnCl₂.

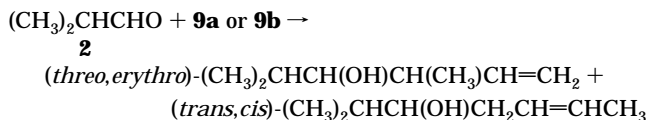
Results and Discussion

Tables 1–4 show the data resulting from the coupling reactions between aldehydes **1–8** and allyl halides **9a** and **9b**. Neither yields nor stereochemical outcomes are affected by changing cosolvents and salts. In fact, reactions can be performed in the absence of cosolvents (see Table 2). Better yields are obtained when **9a** is employed. Yields are found in the range of 60–80% when aldehydes **1–5** are employed (see Tables 1–3). They decrease to 20–40% when α,β-unsaturated aldehydes **6–8** are employed (see Table 4). This is mainly due to

(21) For the isomeric composition of (C₄H₇)Br see ref 20.

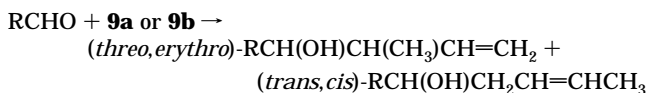
(22) Gambaro, A.; Marton, D.; Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1982**, *226*, 149.

(23) The Sn/Al method refers to the allylation of aldehydes in an ether/water medium by means of allyl bromide under the mediation of tin and aluminum powder; see: Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191.

Table 2. Stereochemical Course of the Reactions between Isobutyraldehyde and Allyl Halides in Cosolvent/H₂O(NH₄Cl)/Zn Medium^a

entry no.	cosolvent	allyl halide	isolated product yield, %	isomeric composition, %		
				<i>threo</i>	<i>erythro</i>	(<i>trans</i> + <i>cis</i>)
1	<i>b</i>	9a	72	74	25	1
2	<i>b</i>	9b	62	77	22	1
3	THF	9a	76	76	23	1
4	THF	9b	66	78	21	1
5	acetonitrile	9a	73	74	25	1
6	acetonitrile	9b	72	76	23	1
7	cyclohexane	9a	77	75	24	1
8 ^c	cyclohexane	9a	75	75	24	1
9	cyclohexane	9b	67	76	23	1
10 ^d	cyclohexane	9b	63	77	21	1

^a Reactions conditions: 0.15 mol of **2** and 0.30 mol of **9a** or **9b**; 25 mL of cosolvent; 50 mL of water (NH₄Cl satd); 0.30 mol of Zn powder. ^b Runs performed without cosolvent. ^c The system has been cooled with an external ice bath. ^d The mixture **9b/2** has been added to the three-phase system cyclohexane/H₂O(NH₄Cl)/Zn.

Table 3. Stereochemical Course of the Reactions between Aldehydes 3–5 and Allyl Halides in Cyclohexane/H₂O(NH₄Cl)/Zn Medium^a

entry no.	RCHO	allyl halide	isolated product yield, %	isomeric composition, %		
				<i>threo</i>	<i>erythro</i>	(<i>trans</i> + <i>cis</i>)
1	3	9a	55	76	20	4
2	3	9a	65	76	20	4
3	3	9b	76	75	22	3
4	4	9a	80	73	26	1
5	4	9b	77	76	24	
6	5	9a	64	42	58	
7	5	9b	55	49	51	

^a Reactions conditions: 0.075 mol of aldehyde and 0.15 mol of **9a** in entry 1; 0.15 mol of aldehyde and 0.30 mol of **9a** or **9b** in entries 2–7; 25 mL of cyclohexane; 50 mL of water (NH₄Cl satd); 0.30 mol of Zn powder.

Table 4. Stereochemical Course of the Reactions between Aldehydes 6–8 and Allyl Halides in Cyclohexane/H₂O(Salt)/Zn Medium^{a,b}

entry no.	salt	RCHO	allyl halide	isolated product yield, %	isomeric composition, %		
					<i>threo</i>	<i>erythro</i>	(<i>trans</i> + <i>cis</i>)
1	NH ₄ Cl	6	9b	13	40	60	
2	NH ₄ Cl	7	9a	20	45	55	
3	NH ₄ Cl	7	9b	24	50	50	
4	NaCl	7	9b	21	49	51	
5	NH ₄ Cl	8	9a	36	43	57	
6	NH ₄ Cl	8	9b	42	45	55	

^a Reactions conditions: 0.15 mol of aldehyde; 0.30 mol of **9a** or **9b**; 25 mL of cyclohexane; 50 mL of water (saturated with salt); 0.30 mol of Zn powder. ^b For the alcoholic isomeric mixtures see Table 3.

side reactions that occur at the expense of the aldehyde. In the case of crotonaldehyde, isomeric mixtures of (*meso, dl*)-2,6-octadiene-4,5-diol were recovered. In the case of benzaldehyde (see Table 3, entries 6 and 7), the low yields of the homoallylic alcohol are also due to the reduction of the carbonyl compound to benzyl alcohol.

Table 5. Comparison of the Stereochemical Results in the Synthesis of β -Methylhomoallylic Alcohols in Aqueous Media by Means of Three Different Methods

alcohol RCH(OH)CH(CH ₃)CH=CH ₂ R	isomeric composition, <i>threo:erythro</i> (yield, %)		
	Zn method ^a	allylstannation method	Sn/Al method ^d
C ₂ H ₅	53:47 (39–81)	60:40 (87) ^b	36:61 (100) Et ₂ O/H ₂ O
(CH ₃) ₂ CH	76:24 (62–77)	78:22 (85) ^c	35:65 (92) Et ₂ O/H ₂ O
(CH ₃) ₃ C	76:24 (55–76)	46:54 (67) ^c	
C ₆ H ₅	42:58 (55–64)	61:39 (85) ^c	40:60 (87) Et ₂ O/H ₂ O 22:78 (81) THF/H ₂ O

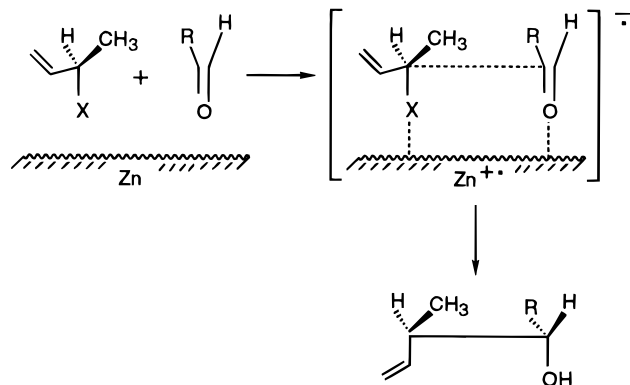
^a Present work. ^b See ref 10. ^c See ref 6. ^d See ref 23.

The same stereochemical results are seen with reagents **9a** and **9b**, showing that the stereochemistry is independent of the geometry of the starting allyl halide. The addition reactions are stereorandom for aldehydes **1**, **5**, and **6–8**, the *threo:erythro* ratio being about 50:50. With aldehydes **2**, **3** and **4**, which bear larger substituents such as (CH₃)₂CH, (CH₃)₃C, and *cyclo*-C₆H₁₁, respectively, moderate stereoselectivity in favor of the *threo*-isomer is observed (*threo:erythro* = 75:25).

To date, aqueous media have been employed in the syntheses of β -methylhomoallylic alcohols, either by direct addition of organometallic reagents generated separately^{6,7} or by allylation of carbonyl compounds *via* mediation of various metals and salts.³ A comparison of the present results with those arising from both allylstannation⁶ and Sn/Al methods is given in Table 5. It is noteworthy that a moderate *threo*-selectivity is seen with both the allylstannation and zinc methods. In contrast, *erythro*-selectivity is favored by the Sn/Al method.

In the case of allylstannation, the activation of the carbonyl group through a coordination step at the tin site²⁴ leads to a pericyclic transition state which explains the moderate *threo*-selectivity when bulky groups are present.²² In the zinc mediated method,^{14–18} intermediate radical ions of the type [CH₂=CHCH(CH₃)X]^{•-} Zn⁺, formed by a one-electron transfer mechanism, are thought to interact with the carbonyl compound. The previously proposed transition state for this Barbier-type reaction, with geometric characteristics similar to those of the corresponding structure in the S_N2 displacement,²⁵ does not explain the observed *threo*-selectivity. In our opinion, the stereochemical results, very similar to those obtained by the allylstannation method (see Table 5), might be better explained through the mechanism proposed as follows.

In the transition state, the more substituted carbon atom (α -carbon) of the allyl moiety interacts with an aldehyde molecule adsorbed on the zinc metal surface. The rigid arrangement of the transition state, having a cyclic structure, favors the *threo*-form due to minor interactions between the methyl group linked to the allyl α -carbon atom and the bulky R group of the aldehyde. Adsorbed carbonyl compounds can interact with the zinc metal to give radical anions and then, by desorption, radical species.^{25,26} As a matter of fact, the encountered side reactions at the expense of the aldehydes **5–8**, such as dimerization and reduction, must be attributed to the formation of radicals [RCHO][•]:²⁷



The hypothesis of a transition state with a cyclic structure might explain the moderate *threo*-selectivity, which is similar to that encountered in the allylstannation case, where the γ -carbon of the allyl group is involved. On the contrary, the *erythro*-selectivity of the Sn/Al method, which requires an oxidative addition of the allyl halide to Sn(0) activated by Al(0), might be explained by invoking an open transition state as previously reported.²⁸

Reactions between isobutyraldehyde and propargyl bromide performed in cyclohexane and water containing various salts are characterized by very low yields (see Table 6). Isomeric mixtures of β -acetylenic and α -allenic alcohols with ratios β : α = 90:10 are recovered. Therefore, also in this case, the major component maintains the acetylenic geometry of the precursor bromide, showing that the aldehyde interacts with the more substituted carbon atom (α -carbon) of the propargyl group.

A different stereochemical course is followed when a substituted propargyl bromide, such as 1-bromo-2-octyne, is used. The α -allenic alcohol is the major component of the recovered isomeric mixture, the ratio being β : α = 30:70. In this case, the initial geometry of the precursor organic bromide is not maintained, showing that a rearrangement of the propargyl unit has occurred during the process.

These findings need to be discussed in light of the results arising from the use of either CH₂=CHCH(CH₃)-Cl (**9a**) or (C₄H₇)Br (**9b**), where the stereochemistry is the same. As a reasonable explanation we hypothesize the formation of radical anions of the sole type [CH₂=CHCH(CH₃)X]^{•-} on the zinc surface. This means that the isomeric *trans*- and *cis*-crotyl bromide also gives

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(27) Comparison of the values affinities shows that unsaturated carbonyl compounds are more able to form carbonyl radical anions than saturated carbonyl compounds. See ref 25.

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Scheme 1. Stereochemical Steps of the Coupling Reactions of Allyl and Propargyl Halides with Aldehydes or Organotins by Means of the Zinc-Mediated Method

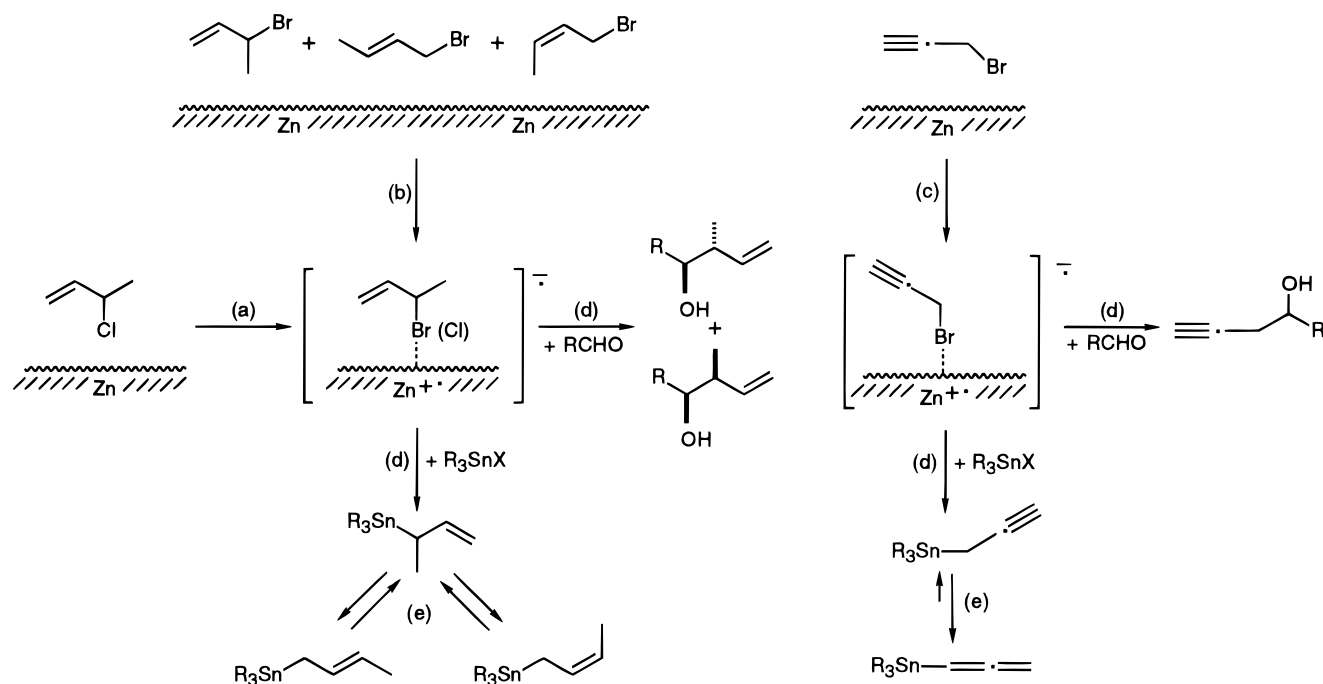
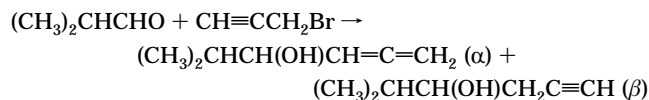


Table 6. Stereochemical Course of the Reactions between Isobutyraldehyde and Propargyl Bromide in Cyclohexane/H₂O(Salt)/Zn Medium^a



entry no.	salt	isolated product yield, %	isomeric composition, %	
			propargyl isomer (β)	allyl isomer (α)
1	NH ₄ Cl	21	91	9
2	NH ₄ Cl	33	89	11
3	ZnCl ₂ ^b	21	91	9
4	c	22	84	16

^a Reactions conditions: 0.15 mol of aldehyde and 0.30 mol of propargyl bromide in entry 1; 0.30 mol of aldehyde and 0.15 mol of propargyl bromide in entries 2–4; 25 mL of cyclohexane; 50 mL of water (saturated with salt); 0.30 mol of Zn powder. ^b ZnCl₂, 5 M. ^c 25 mL of NH₄Cl, 5 M, and 25 mL of NaOH, 5 M, pH = 9.

rise to the above radical anions.²⁹ It is worthy of note that these radical anions with a well-defined geometry are also operating in the reaction between the isomeric mixture (C₄H₇)Br and Bu₃SnCl, the sole recovered isomer being Bu₃SnCH(CH₃)CH=CH₂ when cyclohexane is employed as cosolvent.¹⁸

Scheme 1 summarizes all the results obtained so far by means of the zinc-mediated method for couplings of allyl halides either with aldehydes or triorganotin halides.^{17,18} It accounts for the stereochemistry of the reactions involved. Steps a–c deal with the formation of radical anions *via* an electron transfer from the zinc metal to the organic halide. A rearrangement process must occur in step b because addition of the trapping

reagent, either RCHO or Bu₃SnCl (step d), occurs at the more substituted carbon atom of the radical anion. Isomerization, either of (α -methylallyl)- or propargyltin compounds, takes place only after the coupling processes (equilibria e).¹⁸ Further arguments support the above scheme. Due to the π -electron system, the radical anions have sufficiently long life³⁰ to be trapped on the surface by RCHO or Bu₃SnCl. Trapping of these radical anions must be relatively rapid, otherwise radicals, [CH₂=CH-CHCH₃][•], would be formed. These radicals, adsorbed at the metal surface or diffused freely in solution³¹ after desorption, give rise to side reactions such as couplings or reductions. Actually, when only (α , *trans*, *cis*)-(C₄H₇)-Br (α :*trans*:*cis* = 20:76:4) is allowed to react in a cyclohexane/H₂O(NH₄Cl)/Zn system, a six isomeric mixture of dimeric allyl species with a ratio of α -groups:(*trans* + *cis*) groups = 38:62 is recovered together with other hydrocarbons.

Therefore, the zinc-mediated method can be successfully utilized to prepare either homoallylic alcohols or allyltin derivatives such as allyltriorganotins, allyldiorganotin halides, and/or diallyldiorganotins. We have examined reactions between allyl bromide and equimolar mixtures RCHO/Bu₃SnCl. Results from the systems CH₂=CHCH₂Br/C₂H₅CHO/Bu₃SnCl and CH₂=CHCH₂Br/C₆H₅CHO/Bu₃SnCl show that there is no discrimination between the two coupling reactions 1 and 2, because both homoallylic alcohols and Bu₃SnCH₂CH=CH₂ are isolated. Homoallylic alcohols arise only from the coupling reaction of eq 1, because allyltributyltin formed through reaction 2 is unable to react with aldehydes.³² To the contrary, easy allylstannation of carbonyl compounds can be achieved using allyltin halides neat^{22,24} or in the presence of water.^{4,6} Thus, the system (C₄H₇)Br/(CH₃)₂CHCHO/Bu₂SnCl₂ has been investigated. Results listed in Table

(29) Rearrangements of radicals adsorbed on a metal surface have been thought to occur during Grignard reagent formation, that is during the electron-transfer step. Presently, there is no support about this kind of rearrangement of radical anions. See: Hill, E. A. *J. Organomet. Chem.* **1975**, *91*, 123 and references therein. (b) Walborsky, H. M.; Aronoff, M. S. *J. Organomet. Chem.* **1973**, *51*, 31.

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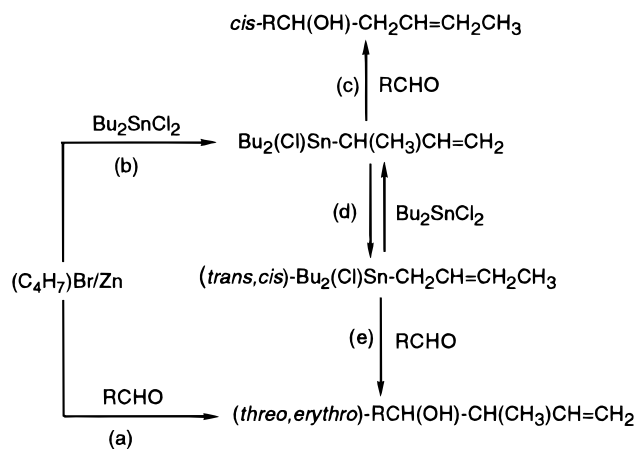
(31) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95.

(32) Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395 and references therein.

Table 7. Stereochemical Course of the Reactions between Isobutyraldehyde (2) and Allyl Halide 9b in Cyclohexane/H₂O(Salt)/Zn/Bu₂SnCl₂ Medium^{a,b}

entry no.	salt	isolated product yield, %	isomeric composition, %			
			<i>threo</i>	<i>erythro</i>	<i>trans</i>	<i>cis</i>
1	NH ₄ Cl	81	65	24	1	10
2	NH=	79	67	23	1	9
	C(NH ₃) ₂ ·HCl					
3	LiClO ₄	78	66	23	1	10
4	LiClO ₄	88	57	25	3	15

^a Reactions conditions: 0.15 mol of **2**; 0.30 mol of **9b**; 25 mL of cyclohexane; 50 mL of water (saturated with salt); 0.30 mol of Zn powder; 0.075 mol of Bu₂SnCl₂ in entries 1–3; 0.15 mol of Bu₂SnCl₂ in entry 4. ^b For the alcoholic isomeric mixtures, see Table 2.

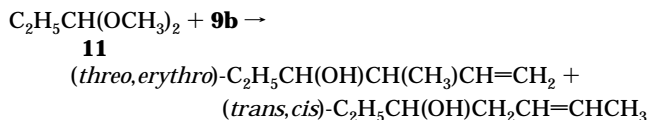
Scheme 2. Schematic Representation of the Overall Process for the System (C₄H₇)Br/(CH₃)₂CHCHO/Bu₂SnCl₂/Zn in Cyclohexane/H₂O (NH₄Cl)

7 show that β -methylhomoallylic alcohols are isolated in high yield (77–88%) without any recovery of allyltin species. The following points are relevant: (a) the isolated alcoholic mixtures contain the four isomers *threo*, *erythro*, *trans*, and *cis* with ratios varying from 66:23:1:10 to 57:25:3:15, respectively; (b) the *cis*-isomer percentage increases with the increase of the amount of Bu₂SnCl₂ (see Table 7, compare entry 4 with entries 1–3); and (c) these mixtures have different isomeric composition with respect to those arising from runs listed in Table 2. Scheme 2 explains these results.

Step a deals with the coupling reaction (see eq 1) forming the (*threo, erythro*)- β -methylhomoallylic alcohols. Step b competes with step a to form Bu₂(Cl)SnCH(CH₃)CH=CH₂. This compound can interact through step c with the aldehyde to give only alcohol in the *cis*-form.³³ Alternatively, it undergoes redistribution with unreacted Bu₂SnCl₂³⁴ to give *trans*- and *cis*-Bu₂(Cl)SnCH₂CH=C-HCH₃ (step d) which react with aldehyde *via* step e to give a mixture of *threo*- and *erythro*- β -methylhomoallylic alcohols. It is noteworthy that the *cis*-alcohol arises only *via* steps b and c, while the *threo*- and *erythro*-alcoholic mixture can be formed through step a, or alternatively *via* steps b, d, and e. We cannot differentiate the extent of the contributions of the two processes leading to the *threo* and *erythro* alcoholic mixture because either step a or steps b, d, and e lead to alcoholic mixtures having

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Table 8. Stereochemical Course of the Reactions between Acetal 11 and Allyl Halide 9b in Cyclohexane/H₂O (LiClO₄, 5 M)/Zn/Bu₂SnCl₂ Medium^a

entry no.	molar ratio acetal:Sn	isolated product yield, %	isomeric composition, %			
			<i>threo</i>	<i>erythro</i>	<i>trans</i>	<i>cis</i>
1	32	55	46	52		2
2	16	58	44	53		3
3	8	65	43	52		5
4	4	52	43	51		6
5	2	63	41	49	2	8
6	1	65	39	45	3	13

^a Reactions conditions: 0.15 mol of **11** in entry 1–5; 0.075 mol of **11** in entry 6; 0.30 mol of **9b**, 25 mL of cyclohexane, 50 mL of salt aqueous solution, and 0.30 mol of Zn powder; 4.7, 9.4, 18.8, 37.5, 75.0, and 75.0 mmol of Bu₂SnCl₂ in entries 1–6, respectively.

the same *ratio* (cf. Table 5). However, we think that step a is prevalent because its rate is certainly greater than the overall rates of steps b, d, and e.

The examined reactions deal with systems where competitive coupling reactions occur. In the system CH₃-CH(OCH₃)₂/(C₄H₇)Br/Bu₂SnCl₂ no competition occurs because only the organotin chloride undergoes the coupling reaction.³⁵ Results from this system are given in Table 8. Homoallylic alcohols are recovered in 50–60% yield as mixtures containing mostly the *threo* and *erythro* isomers together with variable amounts of *cis*-isomer. The content of *cis*-isomer gradually increases from 2 to 13% on account of the increase in Bu₂SnCl₂. In fact, when the organotin dichloride considerably exceeds both the reactants (C₄H₇)Br (**9b**) and acetal,³⁶ the isomeric composition of the recovered mixture is *threo:erythro:trans:cis* = 31:46:1:22. Rates of production of homoallylic alcohols are independent of the Bu₂SnCl₂ amount. Therefore, activation of the allylation process *via* an acid–base interaction of the acetal with Bu₂SnCl₂ can be excluded.³⁷ Thus, allyltin halides produced *via* steps b and d, as shown in Scheme 2, seem to be responsible for the allylation of the acetal, as has been previously found in aqueous medium.⁶

Conclusion

The zinc-mediated method recalls the synthetic procedures based on the heterogeneous reactions occurring at a solid–liquid surface such as the Grignard and Barbier reactions. However, unlike these methods, it makes use of a metal together with a two-phase cosolvent–water (salt) system. The water phase is very important, since the coupling reactions are highly activated by its presence.^{1,2,18} Under such conditions, the zinc particles, located mainly at the boundary surface of the emulsified system, are forced to interact with the allyl bromide, present with the aldehyde in the organic phase,

(35) Under these conditions acetaldehyde- and benzaldehyde dimethyl acetals as well acrolein aldehyde diethyl acetals do not give reactions with the zinc-mediated method.

(36) Using the same amount of entry 43, the mixture acetal/(C₄H₇)Br is added in 25 min to the system cyclohexane/H₂O (LiClO₄)/Zn/Bu₂SnCl₂.

(37) ¹H- and ¹³C-NMR measurements show that acid–base equilibria between Bu₂SnCl₂ and acetal are not operating.

by the high cohesive energy density developed by the water phase.³⁸ Radical ions are formed by a one-electron transfer from zinc metal to (C₄H₇)Br (see Scheme 1). The transfer, accelerated by the high interfacial energy developed by water, occurs under kinetic control. Among the several transition states, the more compact will be favored, with the more negative ΔV^\ddagger .³⁹ Namely, the geometry of a branched allyl group will have a volume smaller than that of *cis*- and *trans*-linear groups. Thus, the branched radical ion adsorbed on the zinc surface will be trapped by the RCHO species to form regioselectively *threo*- and *erythro*- β -methylhomoallylic alcohols. The regioselection encountered in the case of a (C₄H₇)Br mixture is not a unique example, since other substituted allyl bromides such as prenyl always react at the more substituted carbon.^{14,15} On the other hand, regioselection is observed in the case of propargyl substrates, mainly with propargyl bromide. Also, in the case of 1-bromo-2-octyne, the isolated alcoholic mixture is richer in the branched α -allenic alcohols (70%) than the linear β -acetylenic alcohol (30%). Therefore, rearrangements of the organic reactants arise only during the electron-transfer step to give radical anions of well-defined geometry which are responsible for the observed regioselectivity.

With regard to the applicability of this method, in spite of some limitations, it is successful in many cases of addition of allyl and propargyl halides to carbonyl compounds. The method has also been applied to coupling reactions of organotin derivatives with allyl, propargyl, and benzyl bromide. On the basis of its rapidity and convenience together with the possibility of using aqueous commercial solutions, it offers important advantages over other procedures.

Experimental Section

All manipulations were carried out at room temperature, under air atmosphere. Solvents, salts, and zinc powder (325 mesh), commercially available, were used as received. All chemicals, commercially available, were distilled before use. After distillation of technical crotyl bromide, from Aldrich, the resulting product (C₄H₇)Br was an isomeric mixture of α -methylallyl (15%), *trans*-crotyl (76%) and *cis*-crotyl (9%) bromide. Bu₂SnCl₂ was purified by recrystallization before use.

Characterization of all prepared compounds was made by means of IR spectroscopy and ¹³C-NMR. IR spectra were registered as liquid film using KBr optics. ¹³C-NMR spectra of samples were recorded as pure liquid using Me₄Si as internal standard. Analysis of the isolated mixtures was based on the integrated intensities of the appropriate ¹³C-NMR signals, as previously described.^{22,33,40} Quantitative determinations from ¹³C-NMR spectra were made by using sufficient long pulse intervals (at least in the range 20–30 s) in order to avoid saturation of the nuclear spins, together with the gated decoupling method in order to suppress the nuclear Overhauser effect (NOE).⁴¹ Additional GC analyses were performed using a gas-chromatograph equipped with a flame ionization detector (DB 225 polar column, 15 m, 0.25 mm i.d., T_i = 200 °C, T_d = 220 °C, appropriate temperature programmes of the column, T_c were chosen for the analysis of the different alcohols, nitrogen as carrier gas at 10 psi).

Reactions of Aldehydes 1–8 and Allyl Halides 9a and 9b (Tables 1–4). A general procedure has been used in all these cases. In a round-bottom two-necked flask (250 mL)

equipped with a condenser and dropping funnel was added the appropriate aldehyde to a cosolvent/water (salt saturated) mixture. Then, zinc powder was added (quantities are given in Table 1–4). Under magnetic stirring, CH₂=CHCH(CH₃)Cl (9a) or (C₄H₇)Br (9b) (generally in 1:1 stoichiometric ratio with respect to zinc) was added at a rate sufficient to maintain a gentle reflux due the exothermicity of the reactions. The addition lasts about 30–40 min, a time to note the disappearance of the most part of the zinc powder or its total disappearance, as it has been noted in many runs. Then, the progress of the reactions was monitored by means of GC: the complete standing of the product peaks at constant values marked the end of the reactions. Completion of the reactions was verified in a time of about 30–60 min. During this time, formation of a white solid was observed. The solid together with the zinc residue was filtered off, and the cosolvent layer was separated from the aqueous one. Extraction over the aqueous layer was made with two portions (20 mL each) of cyclohexane or ethyl ether. The organic fractions were collected together and dried over Na₂SO₄, and then the organic solution separated from the salt was submitted to fractional distillation. In all cases, the isomeric composition of the isolated alcoholic mixtures was the same as that checked before workup. Yields, listed in Tables 1–4, have been calculated from the amounts of the pure separated mixture of alcohols, and the isomeric compositions have been determined by GC.

3-Methyl-1-hexen-4-ol (Table 1). In all cases, the isolated 3-methyl-1-hexen-4-ol consists of isomeric mixtures having the same ratio, *threo:erythro* = 52:48. These isomeric mixtures have been distilled in the range 110–114 °C/150 mmHg. ¹³C-NMR chemical shifts are in agreement with those already published.²² Yields are greater when NaCl is used (67–81%) with respect to NH₄Cl (39–40%).

3,5-Dimethyl-1-hexen-4-ol (Table 2). The isomeric ratio *threo:erythro* = 75:25 is maintained in all runs independently on the employed cosolvent. An isomeric mixture with a ratio *threo:erythro:(cis+trans)* = 74:24:1 boils in the range 150–156 °C/760 mmHg. ¹³C-NMR chemical shifts are in agreement with those already published.²² Yields are in the range 62–77%.

3,5,5-Trimethyl-1-hexen-4-ol (Table 3, Entries 1–3). Isomeric mixtures of this alcohol have been recovered with a ratio *threo:erythro:(cis+trans)* = 76:20:4. ¹³C-NMR chemical shifts are in agreement with the previous data.²² Yields are in the range 55–76%.

3-Methyl-4-cyclohexyl-1-buten-4-ol (Table 3, Entries 4 and 5). In both cases, the alcoholic mixtures (bp 115 °C/20 mmHg) are recovered in a *threo:erythro* ratio of around 75:25. ¹³C-NMR: *threo*-isomer δ 17.7, 26.4, 26.6, 26.8, 40.7, 41.2, 79.2, 114.8, 140.6; *erythro*-isomer δ 14.9, 26.6, 28.5, 29.9, 40.9, 40.9, 79.0, 113.7, 142.6. Yields are in the range 77–80%.

3-Methyl-4-phenyl-1-buten-4-ol (Table 3, Entries 6 and 7). The isolated mixtures show a *threo:erythro* ratio of 42:58 and 49:51 for entries 6 and 7, respectively. These mixtures boil in the range 93–104 °C/10 mmHg. ¹³C-NMR chemical shifts are in agreement with those previously reported.²² Yields are between 55 and 64%.

3-Methyl-1,5-hexadien-4-ol (Table 4, Entry 1). The isomeric composition is *threo:erythro* = 40:60. ¹³C-NMR chemical shifts are in agreement with the previous data.⁴² The yield in this case is very low, 15%.

***trans*-3-Methyl-1,5-heptadien-4-ol (Table 4, Entries 2–4).** The isomeric ratios *threo:erythro* of the isolated products are about 50:50. ¹³C-NMR chemical shifts are in agreement with the previous data.⁴² Yields are in the range 20–24%. In these cases it has been ascertained that the low yields are mainly due to the dimerization of the crotonaldehyde leading to 1:1 isomeric mixtures of (*meso,dl*)-2,6-octadiene-4,5-diol. A pure sample (4 g) of this compound with an isomeric ratio *meso:dl* = 42:58 (bp 105–107 °C/9 mmHg, (lit.⁴³ 113–114 °C/9 mmHg)) has been isolated from the collected samples. ¹³C-

(38) Water is thought to have a cohesive energy density of 27 kbars. See, Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065.

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NMR chemical shift values are in agreement with those already reported.⁴⁴

trans-3-Methyl-1,5-nonadien-4-ol (Table 4, Entry 5 and 6). In both cases, the isomeric alcoholic mixtures have a *threo:erythro* ratio roughly around 44:56. ¹³C-NMR chemical shifts are in agreement with those previously reported.⁴² Yields are in the range 36–42%.

Reactions of Isobutyraldehyde (2) and Propargyl Bromide (11) (Table 6). The above-described procedure has also been adopted in these cases. The appropriate amount of propargyl bromide was added to the cyclohexane/H₂O (salt)/Zn system using an 80% weight solution in toluene. Therefore, the cosolvent was represented by a mixture of cyclohexane and toluene.

2-Methyl-5-hexyn-3-ol. The isomeric alcoholic mixtures propargyl isomer:allenyl isomer = 90:10 boil in the range 134–136 °C at 760 mmHg. ¹³C-NMR chemical shifts were in agreement with those previously reported.¹⁰ Yields are found in the range 21–33%.

Reactions of Aldehydes 2 and 5 with CH₂=CHCH₂Br in the Presence of Bu₃SnCl. Workup was the same, as above described. Addition of the components was made in the following order: THF (25 mL), H₂O, NH₄Cl saturated (50 mL), aldehyde (0.075 mol), Bu₃SnCl (24.7 g, 0.075 mol), Zn powder (6.5 g, 0.1 mol), then allyl bromide (12.1 g, 0.1 mol). In both runs, nearly equimolar mixtures of homoallylic alcohols and Bu₃SnCH₂CH=CH₂ were obtained.

Reactions of Isobutyraldehyde (2) with (C₄H₇)Br (9b) in the Presence of Bu₂SnCl₂ (Table 7). Reactions between

aldehyde **2** and allyl bromide **9b** were performed in the presence of Bu₂SnCl₂ (quantities are given in Table 7) following the procedure above adopted for the reactions between aldehyde **2** and **5** and CH₂=CHCH₂Br in THF/H₂O (NH₄Cl)/Zn/Bu₃SnCl. Isomeric mixtures of homoallylic alcohols are isolated in very high yields (78–88%) without any recovery of allyltin species. Both diastereomeric pairs were present: (*threo,erythro*)-3,5-dimethyl-1-hexen-4-ol as major product together with a small amount of (*trans,cis*)-3-methyl-5-hexen-3-ol. Indeed, the alcoholic mixtures have an isomeric ratio *threo:erythro:trans:cis* = 66:23:1:10 for entries 1–3 and 57:25:3:15 for entry 4. The increase in *cis*-isomer in entry 4 is related to the increase of the amount of Bu₂SnCl₂.

Reactions of Acetaldehyde Dimethyl Acetal (11) and (C₄H₇)Br (9b) in the Presence of a Catalytic Amount of Bu₂SnCl₂ (Table 8). Following the above procedure, runs have been performed on varying amounts of Bu₂SnCl₂ from 4.7–75 mmol. Yields of homoallylic alcohols are found in the range 52–65%. Under these conditions, the isomeric compositions of the isolated homoallylic alcohols depend on the amount of Bu₂SnCl₂. Indeed, the percentage of the *cis*-CH₃CH(OH)-CH₂CH=CHCH₃ isomer increases from 2 to 13% on varying the molar ratio acetal:Sn from 32 to 1, respectively.

Acknowledgment. We are indebted to the Murst (Rome) and Consiglio Nazionale delle Ricerche (Rome), Progetto Finalizzato Chimica Fine II, for financial support.

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