Efficient Approaches to the Stereoselective Synthesis of Chiral 2-Alkoxydienes and Heterodienes

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Received 28 March 1997

Three approaches to dienes having a chiral alkoxy group at C-2 are shown. Alkoxypropenylphosphonium salts **3** undergo stereoselective Wittig reaction affording high yields of racemic and/or homochiral 2-menthyloxy-, 2-(8-phenylmenthyloxy)-, 2-*trans*-phenylcyclohexyloxy- and 2-*trans*-mesitylcyclohexyloxybuta-1,3-dienes **5a–j** (Method A). Esters derived from chiral alcohols **6** are methylenated with dimethyltitanocene to yield chiral dienes **5a,e,7** (Method B). Chiral α-alkoxyacroleins **8** are prepared by the aza-Wittig reaction of **3** followed by imine hydrolysis and utilized for synthesizing various types of activated chiral alkoxycarbodienes **10,12** and **14** (Method C), as well as 3-alkoxy-1-azabutadiene derivatives **15**.

The Diels–Alder reaction represents probably the most powerful process in synthetic constructions.[1] However, further efforts for developing efficient enantioselective Diels–Alder cycloadditions are still welcome. Certainly, the use of chiral catalysts appears to be a very attractive way for accomplishing such a task and thus it has been elegantly demonstrated in some cases.[1,2]

A different approach for the asymmetric Diels–Alder reaction consists of attaching temporarily an appropriate, removable chiral group (the so-called chiral auxiliary) to either the diene or the dienophile. In this context, whereas a great number of reports dealing with chirally modified dienophiles[1,3] have been released, studies involving homochiral dienes are fewer in number.[1,4] In 1980 Trost et al. reported the synthesis of 1-(*O*-methylmandeloxy)butadiene,[5] later investigated intensively by Thornton et al. to elucidate the stereoselective control elements,[6] and found that it exhibits high facial diastereoselectivity towards various dienophiles; thus, this system can be recognized as the first synthetically useful chiral buta-1,3-diene. Since then a number of dienes with chiral carbon and heteroatom substituents placed at C-1 have been prepared and shown to afford in some cases respectable diastereoselectivities.[7]

Quite surprisingly, very few reports concerning Diels–Alder cycloadditions of chiral 2-heterosubstituted dienes have been reported though they are promising partners in terms of reactivity, facial selectivity and auxiliary removability.[8] Thus, chiral 2-aminobuta-1,3-dienes have proved to be highly useful providing rapid access to optically active six-membered carbo- and heterocycles.[9] More recently, we have communicated that homochiral 2-alkoxydienes are able to cycloadd to carbo- and heterodienophiles with excellent control of the relative and absolute stereochemistry.[10]

Very likely, the main reason for this lack of asymmetric cycloadditions involving chiral heterosubstituted dienes lies in the difficulties associated with their preparation.

In this paper we report the synthesis of chiral 2-alkoxydienes, as well as new azadiene analogs, with different substitution patterns following the approaches shown in Figure 1. First, the synthesis of the target carbodienes is accomplished through the C_3–C_4 double-bond formation which is performed upon the Wittig olefination of chiral 2-alkoxyallylidenephosphoranes with aldehydes (Method A). A second route involving methylenation of α,β-unsaturated esters derived from chiral alcohols with titanium-based reagents (C_1–C_2 double-bond formation) is also reported (Method B). Finally, Method C, the reversal of Method A, is outlined and deals with the Wittig olefination of chiral α-alkoxyacroleins with phosphorous ylids (C_3–C_4 double-bond formation).

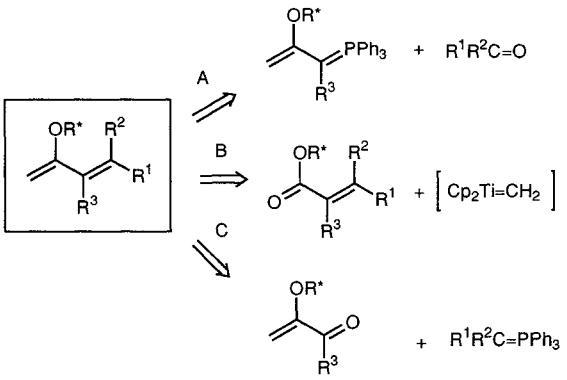

Figure 1

Wittig Olefination of Chiral 2-Alkoxyallylidene(triphenyl)phosphoranes (Method A)

The first approach to the synthesis of chiral 2-alkoxybuta-1,3-dienes is based on a previous procedure from this laboratory for the preparation of 2-aminobuta-1,3-dienes.[11] Accordingly, phosphonium salts **3** were first prepared in nearly quantitative yield by heating at 120 °C a solution of the chiral alcohol **1** and commercially available prop-2-ynyltriphenylphosphonium bromide **(2)** in toluene for 48 hours (Scheme 1). In all cases the crude product was isolated as an essentially pure solid by removal of solvent and precipitation from Et_2O-THF (5:1). Then, a suspension of the triphenylphosphonium salt **3** in THF was treated with potassium hexamethyldisilazide (KHMDS) at −60 °C to generate 2-alkoxyallylidenephosphorane **4** which was reacted overnight with an equimolecular amount of the corresponding aldehyde (25 °C for R = propyl; 60 °C for R = H, phenyl, 2-furyl).

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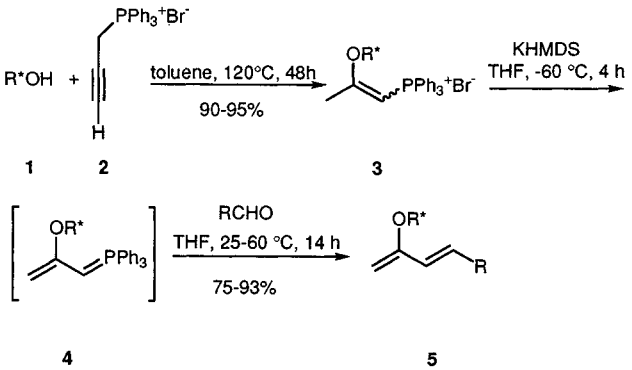
The resulting mixture was subjected to column chromatography affording racemic and enantiomerically pure dienes **5a–j** in very high yields (Table 1). Importantly, the olefination step proved to be totally stereoselective, the *E*-stereoisomer being solely formed ($J_{H(3)-H(4)}$ = 15–16 Hz). We also discovered that if lithium hexamethyldisilazide (LHMDS) is employed, the *E*-diene is produced along with variable amounts (10–15%) of its *Z*-isomer.



	R	R*
(-)-**5a**	Ph	M
(-)-**5b**	H	M
(-)-**5c**	2-Furyl	M
(-)-**5d**	Ph	PM
(±)-**5e**	Ph	PC
(+)-**5e**	Ph	PC
(-)-**5e**	Ph	PC

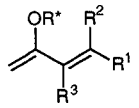
	R	R*
(±)-**5f**	H	PC
(-)-**5f**	H	PC
(±)-**5g**	2-Furyl	PC
(±)-**5h**	Propyl	PC
(±)-**5i**	Ph	MSC
(±)-**5j**	H	MSC

M= (1*R*, 2*S*, 5*R*)-Menthyl
PM= (1*R*, 2*S*, 5*R*)-8-Phenylmenthyl
PC= (1*R*, 2*S*/1*S*, 2*R*)-, (1*R*, 2*S*)- and (1*S*,2*R*)-*trans*-2-phenylcyclohexyl for (±)-**5e-g**, (-)-**5e-f** and (+)-**5e**, respectively
MSC= (1*R*, 2*S*/1*S*, 2*R*)-*trans*-2-mesitylcyclohexyl

Scheme 1

As deduced from Table 1, the Wittig olefination of 2-alkoxyallylidenephosphoranes is a convenient method for the stereoselective synthesis of a variety of chiral 2-alkoxybuta-1,3-dienes with different chiral auxiliaries [ROH = (−)-menthol, (−)-8-phenylmenthol, (±)-, (+)-, and (−)-*trans*-2-phenylcyclohexanol and (±)-*trans*-2-mesitylcyclohexanol] and substituents at C-4 (R = H, aliphatic, aromatic and heteroaromatic).

Table 1. Alkoxy-Substituted Buta-1,3-dienes Prepared



Diene	R^1	R^2	R^3	R*[a]	Yield[b] (Method) (%)
(−)-**5a**[c]	Ph	H	H	M	88 (A) 60 (B)
(−)-**5b**[c]	H	H	H	M	91 (A)
(−)-**5c**[c]	2-Furyl	H	H	M	79 (A)
(−)-**5d**[c]	Ph	H	H	PM	87 (A)
(±)-**5e**	Ph	H	H	PC	93 (A) 56 (B)
(+)-**5e**[c]	Ph	H	H	PC	93 (A) 56 (B)
(−)-**5e**[c]	Ph	H	H	PC	93 (A)
(±)-**5f**	H	H	H	PC	92 (A)
(−)-**5f**[c]	H	H	H	PC	92 (A)
(±)-**5g**	2-Furyl	H	H	PC	90 (A)
(±)-**5h**	Propyl	H	H	PC	76 (A)
(±)-**5i**	Ph	H	H	MSC	86 (A)
(±)-**5j**	H	H	H	MSC	80 (A)
(±)-**7**	H	H	Me	PC	62 (B)
(±)-*E*-**10**	MeO	H	H	PC	90 (C)
(±)-*E*-**12**	PhS	H	H	PC	80 (C)
(±)-*Z*-**12**	H	PhS	H	PC	73 (C)
(±)-**14**	CO_2Et	H	H	PC	80 (C)

[a] For the meaning of the abbreviations M, PM, PC, and MSC see Scheme 1.
[b] Isolated yields after chromatographic purification (deactivated silica gel; Et_2O). All the reported dienes are oils.
[c] $[\alpha]_{20}^{D}$ in CH_2Cl_2: (−)-**5a** −96.9 (*c* = 4.2); (−)-**5b** −86.2 (*c* = 5.1); (−)-**5c** −70.6 (*c* = 6.0); (−)-**5d** −52.9 (*c* = 6.8); (+)-**5e** +97.5 (*c* = 5.9); (−)-**5e** −100.7 (*c* = 6.5); (−)-**5f** −17.3 (*c* = 6.2).

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Biographical Sketch

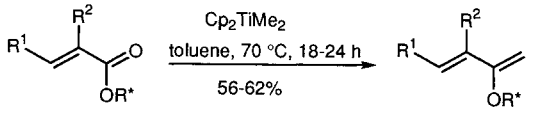
José Barluenga was born in Tardienta, Spain, in 1940. He obtained his Ph.D. degree at the University of Zaragoza in 1966 under the direction of Prof. V. Gómez Aranda. Following this, he spent 3½ years as a postdoctoral research fellow of the Max Planck Gesellschaft at the Max Planck Institut für Kohlenforschung, Mülheim a.d. Ruhr, Germany, in the group of Prof. H. Hoberg working on aluminum chemistry. In 1970 he took a position as a Research Associate at the University of Zaragoza, where he was promoted to Associate Professor in 1972. In 1975 he moved to the University of Oviedo as Professor in Organic Chemistry, where he is now Director of the Instituto Universitario de Química Organometálica "E. Moles". His major research interest is focused on various topics related to selective organic synthesis and organometallic chemistry.

In our opinion two major limitations arise from this strategy. The first one is related to the degree of substitution since neither C-1 nor C-3 substituted dienes seem to be accessible. On the other hand, the failure of phosphorous ylids to give olefination products upon reaction with carboxylic acid derivatives, e.g. esters, makes this procedure unsuitable for synthesizing chiral 1,3-heterodisubstituted dienes.[12]

Titanium-Mediated Methylenation of α,β-Unsaturated Esters Derived from Chiral Alcohols (Method B)

Therefore, we turned our attention to the methylenation reaction of α,β-unsaturated esters (C_1–C_2 double-bond formation) via the well-known methylenetitanocene species (Method B).[13] Though the Tebbe reagent[14] has been shown to be highly useful in synthetic organic chemistry, methylenations of α,β-unsaturated esters derived from chiral alcohols using the easy-to-handle dimethyltitanocene, introduced as a methylenating reagent by Petasis,[15] were first attempted (Scheme 2).

Thus, a number of chiral 2-alkoxybuta-1,3-dienes were alternatively prepared by treatment of the corresponding α,β-unsaturated ester **6** with dimethyltitanocene (3 equiv.) in toluene at 70 °C. Upon completion of the reaction (18–24 h), the crude product was isolated by evaporation of the solvent, precipitation of titanocene oxide by addition of pentane, filtration, and solvent evaporation. In this way, (−)-*E*-menthyl cinnamate and (±)- and (−)-*E*-phenylcyclohexyl cinnamate were methylenated to give 2-alkoxydienes (−)-**5a** (60%), (±)-**5e** (56%) and (−)-**5e** (56%). Several attempts using the Tebbe reagent did not significantly improve these yields. Therefore, it is clear at this point that the synthesis of dienes **5** is more efficiently achieved following the Wittig protocol versus the titanium-based methylenation. However, the latter enabled us to prepare the C-3 substituted diene (±)-**7**, not available by Method A, in 62% isolated yield by methylenation of (±)-phenylcyclohexyl methacrylate with dimethyltitanocene.



6 5a,e, 7

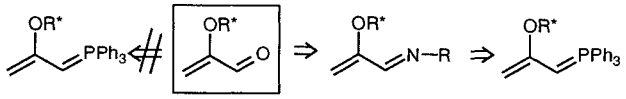
	R¹	R²	R*
(-)-**5a**	Ph	H	M
(±)-**5e**	Ph	H	PC
(-)-**5e**	Ph	H	PC
(±)-**7**	H	Me	PC

Scheme 2

Bearing in mind the flexibility of the titanium-mediated methylenation, e.g. heteroatom substituents in the substrate are tolerated,[15] we realized that this procedure could allow an entry to doubly activated chiral dienes. Unfortunately, the reaction of β-heterosubstituted α,β-unsaturated esters ($R^1 = NR_2$, OMe) with Petasis or Tebbe reagents, under the above reaction conditions, did not lead to the desired dienes; intractable mixtures were obtained in all instances.

Wittig Olefination of Chiral 2-Alkoxyacroleins (Method C)

In the course of the present study, we thought that a new access to chiral dienes, particularly to chiral doubly activated dienes, might be implemented successfully by the Wittig reaction of chiral acrolein derivatives of type **8**. Surprisingly, a literature search revealed that 2-alkoxyacroleins are rather rare compounds which have hardly been synthesized; moreover, no examples of chiral counterparts have yet been reported as far as we are aware.[16] Two retrosynthetic plans to these new chiral captodative olefins were devised as outlined in Figure 2. The simplest one would involve the direct oxidation of phosphorous ylids **4** and the second one, namely the indirect oxidation, would require a two-step process (i) aza-Wittig reaction of **4** with a nitroso compound and (ii) selective hydrolysis of the imine function.



4 8 9 4

Figure 2

We concluded that the first approach does not work at all after trying the oxidation with several oxidizing agents (H_2O_2, peracids, oxygen and dimethyldioxirane).[17] Therefore, we focused on the second retrosynthetic plan **4**→**9**→**8** (Scheme 3). Treatment of a suspension of triphenylphosphonium salts **3** in THF with BuLi at −60 °C followed by addition of an equimolecular amount of dimethylnitrosoethane, Bu^t-N=O,[18] and stirring at room temperature for 48 hours resulted in the formation of the imine derivatives **9** and triphenylphosphine oxide. When the crude reaction was subjected to flash chromatography (silica gel, hexane/ethyl acetate 3:1), selective hydrolysis of the imine moiety took place and the corresponding 2-alkoxyacroleins (−)-**8a** [R*OH = (−)-menthol, 60% yield] and (±)-**8b** [R*OH = (−)-*trans*-phenylcyclohexanol, 62% yield] were isolated as pure, stable oils (Scheme 3). The more representative ^{1}H NMR signals are those due to the olefinic and aldehydic hydrogens which resonate around $\delta = 5.0$ and 5.2 (two doublets, $J = 3.0$ Hz) and $\delta = 9.2$ (singlet), respectively.

Next, the synthesis of doubly activated chiral dienes was carried out by starting with acrolein derivative (±)-**8b** rather than with (−)-**8b**, since it has been demonstrated

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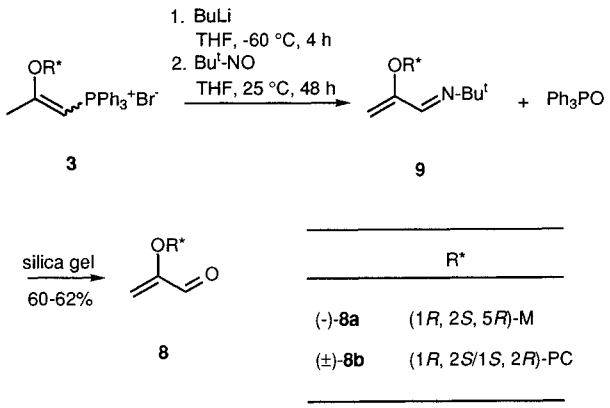
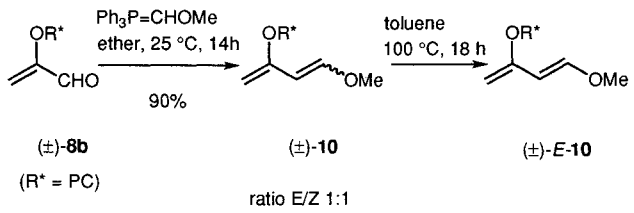


Scheme 3

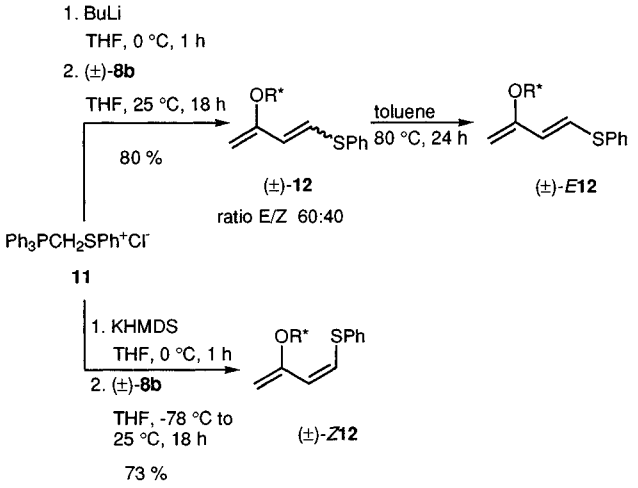
that the phenylcyclohexyl group works more efficiently than the menthyl group in cycloadditions with 2-alkoxydienes[10] (Scheme 4).

First, the "instant ylid" consisting of a commercially available mixture of methoxymethyltriphenylphosphonium bromide and sodium amide[19] was stirred in diethyl ether at 0 °C for 30 minutes. The resulting yellow mixture was treated with compound (±)-**8b** at room temperature furnishing racemic 1-methoxy-3-phenylcyclohexyloxybuta-1,3-diene (**10**) in 90% yield as an ca. 1:1 mixture of *Z*/*E* diastereoisomers ($J_{H-H(cis)}$ = 9.1 Hz; $J_{H-H(trans)}$ = 12.5 Hz). Changes in the reaction conditions (temperature and solvent) or modification of the olefination procedure, e.g. (i) Wittig reaction using triphenylmethoxymethylphosphonium salt and LDA or KHMDS, and (ii) Wittig–Horner reaction using diphenylmethoxymethylphosphine oxide and LDA, did not improve significantly the stereoselectivity of the reaction. It was found, however, that the *E*/*Z* isomers equilibrate in toluene at 100 °C giving rise quantitatively to the more stable diene *E*-**10**.



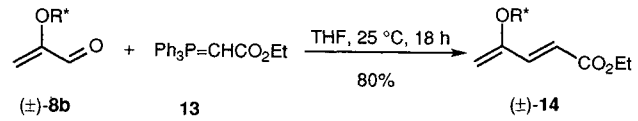
Scheme 4

We also decided to apply this procedure to other appealing activated dienes like those having a sulfur group attached to C-1 (Scheme 5).[20] To this end, the phosphonium salt [Ph_3PCH_2SPh]$^+Cl^-$ **11** was readily prepared from triphenyl phosphine and chloromethylphenylsulfide $ClCH_2SPh$. The olefination of **11** was undertaken in THF using butyllithium (0 °C, 1 h) and the aldehyde (±)-**8b** (25 °C, 18 h) affording a 60:40 mixture of dienes *E*-**12**/*Z*-**12**. This mixture was smoothly transformed into stereochemically pure diene *E*-**12** ($J_{H-H(trans)}$ = 14.9 Hz) by heating at 80 °C in toluene. We also observed in this case that the stereoselectivity of the reaction is strongly dependent on the base used for ylid generation; thus, we found that the successive treatment of the phosphonium salt **11** in THF with KHMDS (0 °C, 1 h) and (±)-**8b** (−78 °C to 25 °C, 18 h) led to the exclusive formation of the diene *Z*-**12** ($J_{H-H(cis)}$ = 10.6 Hz).



Scheme 5

The chiral acrolein **8b** was further employed as intermediate for the synthesis of captodative-type chiral dienes, for instance (±)-**14** (Scheme 6), which are not available directly from phosphonium salts **3** and glyoxylic acid esters (Method A). Thus, the stabilized ylid $Ph_3P{=}CHCO_2Et$ (**13**), generated from the corresponding phosphonium salt and KHMDS, reacted at room temperature with (±)-**8b** to give ethyl *E*-4-phenylcyclohexyloxypenta-2,4-dienoate [(±)-**14**] in 80% yield as the sole stereoisomer.



Scheme 6

Synthesis of Chiral 1-Azadienes from α-Alkoxyacroleins

Electron-donor *N*-substituted-1-azadienes, e.g. 1-dimethylamino-1-azadienes, are considered as highly useful synthons in heterocyclic synthesis primarily because of their ability to undergo [4+2] cycloaddition reactions.[21] Importantly, the lack of suitable entries to the analogous 3-substituted 1-azadienes, and particularly to the homochiral counterparts, has prevented their usefulness being tested, for instance in the field of heterocycloadditions.[22] Accordingly, we have extended the above procedure to the synthesis of the hitherto unknown chiral 3-alkoxy-1-azadiene and 3-alkoxy-1-amino-1-azadiene derivatives (Scheme 7). Thus, stirring a mixture of the 2-alkoxyacroleins **8** and propylamine or *N*,*N*-dimethylhydrazine in diethyl ether at room temperature resulted in the formation of the corresponding chiral 3-alkoxy-1-azadienes **15** in nearly quantitative yield.

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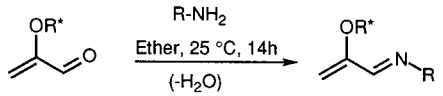

8a,b **15a-c**

	R	R*
(-)-**15a**	Propyl	M
(±)-**15b**	Propyl	PC
(±)-**15c**	Me_2N	PC

Scheme 7

Conclusions

Summarizing, a ready and stereoselective access to racemic and optically active 2-alkoxycarbodienes by olefination of alkoxyallylidenephosphoranes or methylenation of substituted acrylate esters is reported. The alkoxyallylidenephosphoranes also undergo the aza-Wittig olefination and hydrolysis to furnish new alkoxyacroleins which are very convenient precursors of chiral 1-heterosubstituted 3-alkoxydienes[23] and 3-alkoxy-1-azadienes. Since the procedure reported here makes these dienes and heterodienes readily available, and bearing in mind that the simple 2-alkoxycarbodienes work very efficiently in [4+2] cycloadditions,[10] further efforts directed towards their use in enantioselective syntheses are worth undertaking.

NMR spectra were performed on Bruker AC-200 and AC-300 spectrometers using C_6D_6 or $CDCl_3$ as solvents. Mass spectra were determined on a Hewlett-Packard 5987 A spectrometer. All reactions were run under N_2 atmosphere. Flash column chromatography was carried out on silica gel 60 (230–400 mesh). All solvents used were distilled prior to use.

2-Alkoxyprop-1-enyltriphenylphosphonium Bromides 3:
A mixture of the chiral alcohol **1** (20 mmol) and prop-2-ynyltriphenylphosphonium bromide **2** (6.3 g, 16.5 mmol) in toluene (100 mL) was heated at 120 °C for 48 h. Then, the solvent was removed and the crude product precipitated from Et_2O/THF (5:1), filtered, washed with Et_2O and dried in vacuum to give in nearly quantitative yield the alkoxy-substituted triphenylphosphonium salts **3** as essentially pure solids which were used in the olefination processes without further purification.

(1R,2S/1S,2R)-2-[2-(Phenyl)cyclohexyloxy]-1-enyltriphenylphosphonium Bromide:

This compound was isolated as a 90:10 mixture of *Z*/*E* diastereoisomers.

Spectroscopic data for the major isomer:

^{1}H NMR ($CDCl_3$): δ = 7.8–6.8 (m, 20 H), 5.4 (d, J = 17.8 Hz, 1 H), 4.3 (m, 1 H), 2.2 (s, 3 H), 1.9–0.7 (m, 8 H), 0.1 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 176.9 (C), 141.8 (C), 133.5–120.0 (C arom), 81.4 (CH), 76.8 (CH, d, $^1J_{PC}$ = 96.4 Hz), 48.8 (CH), 33.7 (CH_2), 31.9 (CH_2), 24.5 (CH_2), 23.5 (CH_2), 20.3 (CH_3).

^{31}P NMR ($CDCl_3$): δ = 12.2.

2-Alkoxybuta-1,3-dienes 5a–j by Wittig Olefination of 2-Alkoxyallylidene(triphenyl)phosphoranes 4 (Method A); General Procedure:
A 0.5 M solution of KHMDS [$(Me_3Si)_2NK$] in toluene (12 mL, 6 mmol) was added at −60 °C under N_2 to a suspension of the triphenylphosphonium salt **3** (5 mmol) in THF (60 mL). The resulting dark solution was stirred at this temperature for 4 h, then the bath was removed and the mixture stirred at 25 °C for 1 h. To the resulting solution was added at −40 °C the corresponding aldehyde RCHO (6 mmol) or paraformaldehyde (excess, 0.54 g). After 30 min at −40 °C the mixture was stirred overnight (25 °C for R = propyl; 60 °C for R = H, phenyl, 2-furyl). The mixture was cooled and the solvents were removed in vacuum. The resulting residue was treated successively with anhyd pentane (50 mL) and anhyd Et_2O (5 mL) and the solid was filtered off under N_2. The solvent was removed and the residue purified by column chromatography (deactivated silica gel; Et_2O) to give 2-alkoxydienes **5a–j** as clear oils. Dienes **5a**, **b**, **e** and **f** were further purified by high-vacuum distillation. Reaction yields and [α] values for the non-racemic systems are given in Table 1 and spectroscopic data are collected in Table 2.

Titanium-Mediated Methylenation of α,β-Unsaturated Esters (Method B): Synthesis of 2-Alkoxybuta-1,3-dienes (−)-5a, (±)-5e, (−)-5e, and (±)-7; General Procedure:
A mixture of α,β-unsaturated ester **6** (6 mmol) and dimethyltitanocene (3.7 g, 18 mmol) in toluene (20 mL) was stirred at 70 °C for 18–24 h under N_2 with the exclusion of light. The crude reaction was concentrated under vacuum to a viscous brown oil, pentane (10 mL) was added and the titanium species filtered off. The residue was purified by column chromatography (deactivated silica gel; Et_2O) to afford 2-alkoxydienes (−)-**5a**, (±)-**5e**, (−)-**5e**, and (±)-**7** as clear oils. Dienes (−)-**5a**, (±)-**5e**, and (−)-**5e** were further purified by high-vacuum distillation. Reaction yields and spectroscopic data are collected in Table 1 and 2, respectively.

2-Alkoxyacroleins 8a,b from Triphenylphosphonium Salts 3:
A 1.6 M solution of BuLi in hexane (3.8 mL, 6.1 mmol) was added at −60 °C under N_2 to a suspension of the triphenylphosphonium salt **3** (R* = M and R* = PC) (5 mmol) in THF (60 mL). The resulting dark solution was stirred at this temperature for 4 h; then, the bath was removed and the mixture stirred at 25 °C for 1 h. Dimethylnitrosoethane, Bu^t-N=O, (0.43 g, 5 mmol) was added to the resulting solution at −40 °C and stirred at 25 °C for 48 h. The mixture was shaken with H_2O (30 mL), extracted with CH_2Cl_2 and dried (Na_2SO_4). The resulting mixture containing the imine derivative **9** and triphenylphosphine oxide was subjected to flash chromatography (silica gel, hexane/EtOAc 3:1) to give the 2-alkoxyacroleins (−)-**8a** (0.63 g, 60%) and (±)-**8b** (0.66 g, 62%) as pure oils. Compounds **8** were stored at −10 °C for several weeks without any sign of decomposition.

(−)-(1R,2S,5R)-2-Menthyloxypropenal **[(−)-8a]**: $[\alpha]_{20}^{D}$ in CH_2Cl_2: −65.9 (c = 6.1).

^{1}H NMR ($CDCl_3$): δ = 9.2 (s, 1 H), 5.2 (d, J = 3.0 Hz, 1 H), 5.0 (d, J = 3.0 Hz, 1 H), 3.8 (m, 1 H), 2.0 (m, 2 H), 1.7–0.8 (m, 13 H), 0.7 (d, J = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 188.8, 157.3, 103.1, 77.6, 47.1, 38.5, 34.1, 31.1, 25.7, 23.3, 21.9, 20.3, 16.2.

(±)-(1R,2S/1S,2R)-2-[2-(Phenyl)cyclohexyloxy]propenal **[(±)-8b]**:

^{1}H NMR ($CDCl_3$): δ = 9.0 (s, 1 H), 7.3–7.1 (m, 5 H), 5.0 (d, J = 3.0 Hz, 1 H), 4.9 (d, J = 3.0 Hz, 1 H), 4.1 (m, 1 H), 2.9 (m, 1 H), 2.3–1.3 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 188.3 (d), 157.0 (s), 142.9 (s), 127.9 (d), 127.3 (d), 126.0 (d), 103.2 (t), 80.1 (d), 49.5 (d), 33.1 (t), 30.6 (t), 25.5 (t), 24.4 (t).

Wittig Olefination of α-Alkoxyacrolein 8b (Method C): Synthesis of Alkoxybuta-1,3-dienes 10, 12 and 14:

(*E*)-1-Methoxy-3-(2-phenylcyclohexyloxy)buta-1,3-diene [(*E*)-10]:
A commercially available mixture of methoxymethyltriphenylphosphonium bromide and sodium amide (1 g, ≈ 2.3 mmol of the phosphonium salt) in Et_2O (40 mL) was stirred at 0 °C for 30 min. Afterwards, 2-alkoxyacrolein (±)-**8b** (0.49 g, 2.3 mmol) was added, the mixture was stirred at 25 °C for 14 h and the solvent removed under

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Table 2. Spectral Data of Alkoxy-Substituted Buta-1,3-dienes **5**, **7**, **10**, **12**, and **14**

Diene	^{1}H NMR (C_6D_6) δ, J (Hz)	^{13}C NMR (C_6D_6) δ	MS M^+ (%)
5a[a]	7.5–7.2 (m, 5H), 6.9 (d, J = 16.0, 1H), 6.6 (d, J = 16.0, 1H), 4.3 (s, 2H), 4.0 (m, 1H), 2.3 (m, 2H), 1.8–1.5 (m, 5H), 1.2–1.0 (m, 8H), 0.9 (d, J = 6.9, 3H)	156.9 (s), 136.8 (s), 128.4 (d), 128.1 (d), 127.4 (d), 126.5 (d), 125.8 (d), 87.5 (t), 76.3 (d), 47.8 (d), 39.4 (t), 34.5 (t), 31.2 (d), 26.2 (d), 23.7 (t), 22.1 (q), 20.6 (q), 16.7 (q)	284 (37)
5b	6.2 (dd, J = 17, 10, 1H), 5.9 (dd, J = 17, 2, 1H), 5.1 (br d, J = 10, 1H), 4.23 (s, 1H), 4.21 (s, 1H), 3.9 (m, 1H), 2.3 (m, 2H), 1.7–0.8 (m, 16H)	157.3 (s), 134.7 (d), 114.0 (t), 87.0 (t), 76.3 (d), 48.2 (d), 39.7 (t), 34.8 (t), 31.4 (d), 26.7 (d), 24.2 (t), 22.3 (q), 20.8 (q), 17.1 (q)	208 (41)
5c	7.3 (s, 1H), 7.25 (d, J = 15.7, 1H), 6.9 (d, J = 15.7, 1H), 6.2 (m, 2H), 4.40 (s, 1H), 4.39 (s, 1H), 4.0 (m, 1H), 2.4 (m, 2H), 1.7–0.9 (m, 16H)	157.1 (s), 153.4 (s), 142.4 (d), 125.0 (d), 116.9 (d), 111.8 (d), 109.3 (d), 88.1 (t), 76.4 (d), 48.3 (d), 39.8 (t), 34.8 (t), 31.4 (d), 26.7 (d), 24.1 (t), 22.3 (q), 20.8 (q), 17.0 (q)	274 (29)
5d	7.4–7.0 (m, 10H), 6.7 (d, J = 15.9, 1H), 6.5 (d, J = 15.9, 1H), 4.3 (s, 1H), 4.2 (s, 1H), 4.0 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.5 (s, 3H), 1.3 (s, 3H), 1.2–0.9 (m, 6H), 0.7 (d, 3H)	157.0 (s), 152.1 (s), 138.1 (s), 129.8 (d), 129.5 (d), 128.9 (d), 128.5 (d), 128.4 (d), 127.9 (d), 126.8 (d), 126.2 (d), 88.0 (t), 77.4 (d), 52.4 (d), 40.9 (s), 40.4 (t), 35.8 (t), 32.0 (d), 28.6 (q), 28.0 (t), 27.4 (q), 22.7 (q)	360 (24)
5e[a]	7.5–7.2 (m, 10H), 6.7 (d, J = 15.8, 1H), 6.4 (d, J = 15.8, 1H), 4.3 (d, J = 1.8, 1H), 4.25 (d, J = 1.8, 1H), 4.2 (m, 1H), 2.9 (m, 1H), 2.3–1.3 (m, 8H)	157.2 (s), 143.9 (s), 136.8 (s), 128.4 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.7 (d), 126.9 (d), 126.0 (d), 125.2 (d), 88.1 (t), 79.4 (d), 50.4 (d), 33.8 (t), 31.4 (t), 25.9 (t), 24.6 (t)	304 (46)
5f	7.3–7.1 (m, 5H), 5.9 (dd, J = 17, 10, 1H), 5.6 (dd, J = 17, 2, 1H), 4.7 (br d, J = 10, 1H), 4.1 (s, 1H), 4.0 (m, 2H), 2.7 (m, 1H), 2.3–1.1 (m, 8H)	158.0 (s), 144.3 (s), 134.5 (d), 129.1 (d), 127.9 (d), 126.7 (d), 114.1 (t), 87.4 (t), 79.2 (d), 51.1 (d), 34.3 (t), 31.6 (t), 26.2 (t), 25.0 (t)	228 (51)
5g	7.3–6.9 (m, 6H), 6.7 (d, J = 14.9, 1H), 6.5 (d, J = 14.9, 1H), 6.0 (m, 2H), 4.15 (d, J = 1.8, 1H), 4.10 (d, J = 1.8, 1H), 4.0 (m, 1H), 2.7 (m, 1H), 2.3 (m, 1H), 1.8–1.0 (m, 7H)	158.2 (s), 154.0 (s), 144.7 (s), 142.3 (d), 129.1 (d), 127.9 (d), 126.6 (d), 124.3 (d), 117.4 (d), 112.0 (d), 109.1 (d), 88.9 (t), 79.8 (d), 50.1 (d), 34.5 (t), 32.1 (t), 26.7 (t), 24.6 (t)	294 (21)
5h	7.2–7.0 (m, 5H), 6.0 (m, 1H), 5.7 (d, J = 15.2, 1H), 4.0 (m, 3H), 2.7 (m, 1H), 2.3 (m, 1H), 1.9–0.8 (m, 11H), 0.7 (t, J = 7.0, 3H)	157.8 (s), 144.6 (s), 132.8 (d), 129.0 (d), 127.8 (d), 126.3 (d), 122.4 (d), 85.2 (t), 79.0 (d), 50.9 (d), 34.3 (t), 33.8 (t), 31.7 (t), 26.3 (t), 22.5 (t), 19.4 (t), 13.8 (q)	270 (45)
5i	7.4–7.0 (m, 5H), 6.9 (s, 1H), 6.8 (d, J = 14.9, 1H), 6.7 (s, 1H), 6.4 (d, J = 14.9, 1H), 4.8 (m, 1H), 4.3 (s, 1H), 4.2 (s, 1H), 3.5 (m, 1H), 2.5 (s, 3H), 2.4 (s, 3H), 2.1 (s, 3H), 1.9–1.2 (m, 8H)	158.2 (s), 142.5 (d), 137.4 (s), 137.0 (s), 136.5 (s), 135.6 (s), 134.9 (s), 129.0 (d), 128.4 (d), 127.6 (d), 127.4 (d), 127.0 (d), 125.9 (d), 88.1 (t), 77.8 (d), 47.1 (d), 33.1 (t), 30.5 (t), 27.0 (t), 25.1 (t), 22.1 (q), 21.9 (q), 20.7 (q)	346 (47)
5j	6.8 (s, 1H), 6.6 (s, 1H), 5.9 (dd, J = 17, 10, 1H), 5.4 (dd, J = 17, 2, 1H), 4.8 (br d, J = 10, 1H), 4.6 (m, 1H), 4.1 (s, 1H), 4.0 (s, 1H), 3.3 (m, 1H), 2.4 (s, 3H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0–1.0 (m, 8H)	157.5 (s), 136.5 (s), 135.3 (s), 134.8 (s), 134.3 (d), 132.3 (s), 131.6 (d), 129.6 (d), 114.1 (t), 86.9 (t), 76.8 (d), 46.8 (d), 32.5 (t), 30.6 (t), 27.0 (t), 25.0 (t), 22.1 (q), 21.9 (q), 20.8 (q)	270 (31)
7	7.3–7.0 (m, 5H), 5.5 (d, J = 2, 1H), 4.8 (s, 1H), 4.3 (d, J = 2, 1H), 4.1 (s, 1H), 4.0 (m, 1H), 2.7 (m, 1H), 2.3 (m, 1H), 1.7 (s, 3H), 1.6–1.0 (m, 7H)	157.9 (s), 144.8 (s), 138.0 (s), 129.0 (d), 127.8 (d), 126.6 (d), 114.8 (t), 87.6 (t), 79.4 (d), 50.7 (d), 34.0 (t), 31.2 (t), 26.0 (t), 24.8 (t), 17.1 (q)	242 (11)
E-**10**	7.3–7.1 (m, 5H), 7.0 (d, J = 12.5, 1H), 5.2 (d, J = 12.5, 1H), 4.2 (m, 1H), 4.1 (s, 1H), 4.0 (s, 1H), 3.0 (s, 3H), 2.7 (m, 1H), 2.5 (m, 1H), 1.9–1.1 (m, 7H)	157.3 (s), 150.1 (d), 144.4 (s), 128.5 (d), 127.7 (d), 126.4 (d), 102.5 (d), 82.5 (t), 78.9 (d), 55.5 (q), 50.9 (d), 34.4 (t), 31.2 (t), 26.3 (t), 24.9 (t)	258 (8)
E-**12**	7.2–6.9 (m, 10H), 6.8 (d, J = 14.9, 1H), 6.0 (d, J = 14.9, 1H), 4.0 (m, 2H), 3.85 (d, J = 1.8, 1H), 2.6 (m, 1H), 2.2–1.0 (m, 8H)	156.6 (s), 144.3 (s), 134.7 (s), 132.4 (d), 129.3 (d), 128.8 (d), 128.5 (d), 128.3 (d), 127.9 (d), 127.7 (d), 124.5 (d), 86.7 (t), 79.4 (d), 50.8 (d), 34.1 (t), 31.6 (t), 26.2 (t), 24.8 (t)	336 (17)
Z-**12**	7.4–7.0 (m, 10H), 6.1 (d, J = 10.6, 1H), 5.7 (d, J = 10.6, 1H), 4.3 (s, 2H), 4.2 (m, 1H), 3.0 (m, 1H), 2.2–1.1 (m, 8H)	157.7 (s), 144.4 (s), 138.5 (s), 131.6 (d), 128.4 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.0 (d), 126.4 (d), 122.6 (d), 87.3 (t), 79.1 (d), 50.5 (d), 34.4 (t), 31.4 (t), 26.2 (t), 24.9 (t)	336 (41)
14	7.3–7.0 (m, 6H), 6.45 (d, J = 15, 1H), 4.19 (d, J = 1.5, 1H), 4.12 (d, J = 1.5, 1H), 4.0 (m, 3H), 2.6 (m, 1H), 2.3–1.0 (m, 8H), 0.9 (t, J = 7.1, 3H)	166.4 (s), 155.8 (s), 143.9 (s), 141.2 (d), 129.1 (d), 127.9 (d), 126.6 (d), 119.4 (d), 93.8 (t), 79.5 (d), 60.1 (t), 50.5 (d), 33.8 (t), 31.2 (t), 26.1 (t), 24.7 (t), 14.2 (q)	300 (15)

[a] NMR spectra recorded in $CDCl_3$.

reduced pressure. The residue was treated with anhyd pentane (10 mL), the solid was filtered off under N_2 and the solvent removed to give an ca. 1:1 mixture of (*E*)-**10**/(*Z*)-**10**. This mixture was taken up in anhyd toluene (10 mL) and stirred at 100 °C for 18 h. The solvent was removed under reduced pressure to give (*E*)-**10** as a yellowish oil which was further purified by high-vacuum distillation (0.5 g, 90 % yield). The spectroscopic data of compound (*E*)-**10** are collected in Table 2.

(*E*)-3-(2-Phenylcyclohexyloxy)-1-phenylsulfanylbuta-1,3-diene [(*E*)-12]:

A 1.6 M solution of BuLi in hexane (0.19 mL, 0.30 mmol) was added at 0 °C under N_2 to a suspension of the triphenylphosphonium salt **11** (126 mg, 0.30 mmol) in THF (5 mL). After the resulting solution had been stirred for 1 h, 2-alkoxyacrolein (±)-**8b** (64 mg, 0.30 mmol) was added and stirring continued overnight at 25 °C. Removal of the solvents in vacuo furnished a residue which was treated with anhyd pentane (5 mL) and filtered under N_2 to give a 60:40 mixture of (*E*)-**12**/(*Z*)-**12**. This mixture was taken up in anhyd toluene (5 mL) and stirred at 80 °C for 24 h. The solvent was removed under vacuum to afford the diene (*E*)-**12** as a yellow oil (77 mg, 80 % yield). The spectroscopic data of compound (*E*)-**12** are collected in Table 2.

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(*Z*)-3-(2-Phenylcyclohexyloxy)-1-phenylsulfanylbuta-1,3-diene [(*Z*)-12]:
A 0.5 M solution of KHMDS [$(Me_3Si)_2NK$] in toluene (0.7 mL, 0.35 mmol) was added at 0 °C under N_2 to a suspension of the triphenylphosphonium salt **11** (126 mg, 0.30 mmol) in THF (10 mL). After the resulting solution had been stirred for 1 h, 2-alkoxyacrolein (±)-**8b** (64 mg, 0.30 mmol) was added at −78 °C and stirring continued overnight at 25 °C. Removal of the solvents in vacuo furnished a residue which was treated with anhyd pentane (10 mL) and filtered under N_2 to give the diene (*Z*)-**12** (70 mg, 73 % yield). The spectroscopic data of compound (*E*)-**12** are collected in Table 2.

Ethyl (*E*)-4-(2-Phenylcyclohexyloxy)penta-2,4-dienoate (14):
A 0.5 M solution of KHMDS [$(Me_3Si)_2NK$] in toluene (1 mL, 0.5 mmol) was added at 0 °C under N_2 to a suspension of the triphenylphosphonium salt $(Ph_3PCH_2CO_2Et)^+Br^-$ (215 mg, 0.5 mmol) in THF (10 mL). The resulting solution was stirred at this temperature for 1 h, then 2-alkoxyacrolein (±)-**8b** (107 mg, 0.5 mmol) was added and the mixture was stirred overnight at 25 °C. Afterwards, the solvents were removed in vacuo, the residue treated with anhyd pentane (5 mL) and the solid filtered under N_2. Removal of the solvents followed by column chromatography (deactivated silica gel; Et_2O) led to diene **14** (113 mg, 80 %). The spectroscopic data of compound (*E*)-**14** are collected in Table 2.

3-Alkoxy-1-azabuta-1,3-dienes 15 from Chiral 2-Alkoxyacroleins; General Procedure:
To a solution of the 2-alkoxyacroleins (−)-**8a** and (±)-**8b** (2 mmol) in Et_2O (10 mL) was added an equimolecular amount of propylamine (for compounds **15a** and **15b**) or *N*,*N*-dimethylhydrazine (for compound **15c**). The mixture was stirred at 25 °C for 14 h, the solvent removed and the remaining liquid purified by high-vacuum distillation to give pure azadienes **15a–c**.

(−)-(1R,2S,5R)-3-Menthyloxy-1-propyl-1-azabuta-1,3-diene [(−)-**15a**]: yield: 0.45 g (90 %); $[\alpha]_{20}^{D}$ in CH_2Cl_2 (c/mg cm^{-3}): −88.2 (c = 5.6).

^{1}H NMR ($CDCl_3$): δ = 7.6 (s, 1 H), 4.54 (d, J = 2.2 Hz, 1 H), 4.50 (d, J = 2.2 Hz, 1 H), 3.8 (m, 1 H), 3.4 (m, 2 H), 2.1 (m, 2 H), 1.6–0.8 (m, 18 H), 0.7 (d, J = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 158.3 (d), 156.7 (s), 92.7 (t), 77.3 (d), 63.1, (t), 47.0 (d), 39.0 (t), 34.3 (t), 31.3 (d), 25.9 (d), 23.7 (t), 23.6 (t), 22.0 (q), 20.4 (q), 16.5 (q), 11.6 (q).

(±)-(1R,2S/1S,2R)-3-[2-(Phenyl)cyclohexyloxy]-1-propyl-1-azabuta-1,3-diene [(±)-**15b**]: yield: 0.47 g (92 %).

^{1}H NMR ($CDCl_3$): δ = 7.4 (s, 1 H), 7.3–7.1 (m, 5 H), 4.45 (d, J = 2.2 Hz, 1 H), 4.37 (d, J = 2.2 Hz, 1 H), 4.1 (m, 1 H), 3.5 (m, 1 H), 3.3 (m, 1 H), 2.9 (m, 1 H), 2.4–1.2 (m, 10 H), 0.8 (t, J = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 157.9 (d), 156.6 (s), 143.6 (s), 127.8 (d), 127.6 (d), 125.9 (d), 92.5 (t), 79.9 (d), 62.9 (t), 49.5 (d), 33.4 (t), 31.0 (t), 25.8 (t), 24.8 (t), 23.5 (t), 11.6 (q).

(±)-1-Dimethylamino-(1R,2S/1S,2R)-3-[2-(phenyl)cyclohexyloxy]-1-azabuta-1,3-diene [(±)-**15c**]: yield: 0.48 g (94 %).

^{1}H NMR ($CDCl_3$): δ = 7.4–7.2 (m, 5 H), 6.4 (s, 1 H), 4.4 (d, J = 1.8 Hz, 1 H), 4.15 (m, 1 H), 4.09 (d, J = 1.8 Hz, 1 H), 2.8 (s, 6 H), 2.5–1.3 (m, 9 H).

^{13}C NMR ($CDCl_3$): δ = 156.9 (s), 143.8 (s), 129.7 (d), 127.8 (d), 127.6 (d), 125.8 (d), 84.5 (t), 79.5 (d), 49.8 (d), 42.4 (q), 33.8 (t), 31.1 (t), 25.9 (t), 24.7 (t).

We thank the Ministerio de Educación y Ciencia for financial support (DGICYT, PB92.1005 and PB94-1313) and for research grants to L. A. L. and A. S.-S. We also thank Prof. Dr. M. Regitz for interesting discussions and valuable suggestions and the undergraduate students S. Martínez and S. Sánchez for performing some experiments.

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