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Synthesis of Variously 2-Substituted Alkyl (*Z*)- and (*E*)-2-Alkenoates and (*Z*)- and (*E*)-α-Ylidene-γ-butyrolactones via Palladium-Mediated Cross-Coupling Reactions between Organostannanes and Organic Halides

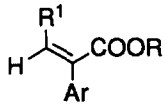
Fabio Bellina, Adriano Carpita, Massimo De Santis# and Renzo Rossi *

Dipartimento di Chimica e Chimica Industriale – University of Pisa – Via Risorgimento 35, I-56126 Pisa, Italy

Abstract: Stereoisomerically pure trisubstituted α,β-unsaturated esters of general formula **7** have been efficiently synthetized using two different protocols. The first one involves the palladium(0)/copper(I)-mediated cross-coupling reaction between alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**2**, and aryl or alkenyl iodides. The second protocol, which allows to prepare stereodefined 2-aryl, 2-methyl, 2-(1-alkenyl) as well as 2-acyl substituted α,β-unsaturated esters, is based on the cross-coupling reaction between easily available alkyl (*Z*)- or (*E*)-2-halo-2-alkenoates and organostannanes in NMP, in the presence of catalytic amounts of $PdCl_2(PhCN)_2$, $AsPh_3$ and CuI. (*Z*)-and (*E*)-2-ethenyl substituted α,β-unsaturated esters prepared according to this procedure have been proven to be useful precursors to (*Z*)- and (*E*)-α-ylidene-γ-butyrolactones, (*Z*)- and (*E*)-**8**, respectively.

Trisubstituted α,β-unsaturated esters are an important class of compounds as synthetic intermediates of many naturally-occurring substances. Stereoselective construction of such esters is a fundamental challenge in organic synthesis[1].

In the context of our studies on the synthesis and applications of 1-alkenylstannanes bearing a functional substituent in 1-position, in 1992 we reported that stereodefined 2-(hetero)aryl substituted alkyl 2-alkenoates of general formula **1** could be efficiently prepared by a reaction sequence involving: (i) the palladium(0)-mediated hydrostannylation of alkyl 2-alkynoates; (ii) iododestannylation of stereoisomerically pure alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**2**, so obtained; and (iii) the palladium(0)-mediated reaction between the resulting alkyl (*E*)-2-iodo-2-alkenoates, (*E*)-**3**, and (hetero)arylzinc halides[2].



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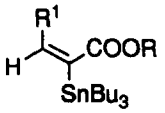
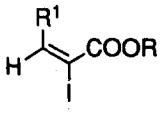
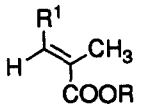


(*E*)-**2**



(*E*)-**3**



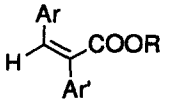
(*E*)-**4**

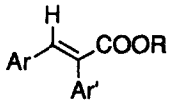
(R^1 = alkyl, aryl; R = Me, Et)

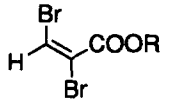
In partial fulfilment of his PhD thesis
* To whom correspondence should be addressed

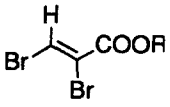
Moreover, we showed that, on treatment of compounds (*E*)-**3** with a fourfold excess of $(CH_3)_2CuLi$ in Et_2O at -78 °C, followed by reaction with a large excess of methyl iodide in the presence of HMPA, alkyl (*E*)-2-methyl-2-alkenoates, (*E*)-**4**, having very high stereoisomeric purity could be obtained in high yield[2].

More recently, our continuing interest in this area spurred us to develop a new highly selective and effective protocol for the preparation of stereoisomerically pure unsymmetrically 2,3-di(hetero)aryl substituted alkyl (*Z*)- and (*E*)-propenoates, (*Z*)- and (*E*)-**5**[3]. Such protocol involves two consecutive palladium(0)-mediated (hetero)arylations of easily available alkyl (*E*)- and (*Z*)-2,3-dibromopropenoates, (*E*)- and (*Z*)-**6**, using (hetero)arylzinc halides as (hetero)arylation reagents[3].

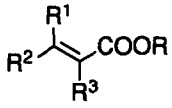

(*Z*)-**5**


(*E*)-**5**


(*E*)-**6**

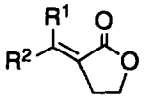

(*Z*)-**6**

As an extension of these investigations, we now disclose here two novel and effective synthetic routes to variously 2-substituted alkyl (*Z*)- and (*E*)-2-alkenoates of general formula **7**, which are based on palladium-mediated cross-coupling reactions between organostannanes and organic halides.



(*Z*)-**7** : R^1 = alkyl, aryl; R^2 = H; R^3 = alkenyl, aryl, $COCH_3$, Me; R = Me, Et
(*E*)-**7** : R^1 = H; R^2 = alkyl, aryl; R^3 = alkenyl, aryl; R = Me, Et

Furthermore, we report that alkyl (*Z*)- and (*E*)-2-ethenyl-2-alkenoates, which are included among these stereodefined esters **7**, are useful intermediates in a simple and quite efficient synthesis of (*Z*)- and (*E*)-α-ylidene-γ-butyrolactones, (*Z*)- and (*E*)-**8**, respectively.



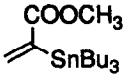
(*Z*)-**8** : R^1 = alkyl, aryl; R^2 = H
(*E*)-**8** : R^1 = H; R^2 = alkyl, aryl

RESULTS AND DISCUSSION

A) Synthesis of stereodefined trisubstituted α,β-unsaturated esters

As previously reported[2], attempts to prepare alkyl 2-(hetero)aryl-2-alkenoates of general formula **1** by reaction between alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**2**, and 1.1 equiv of (hetero)aryl iodides in refluxing THF, in the presence of catalytic amounts of palladium catalysts such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, failed. However, quite recently it has been shown that methyl 2-tributylstannylpropenoate, **9**, is able to undergo a cross-coupling reaction with 0.4 equiv of aryl iodides or triflates in DMF at room

temperature, in the presence of 10 mol % of $Pd(PPh_3)_4$ and 0.75 equiv of CuI, to give the corresponding 2-aryl propenoic esters, **10**, in satisfactory yields[4].



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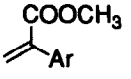

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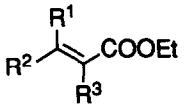
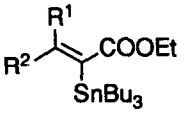


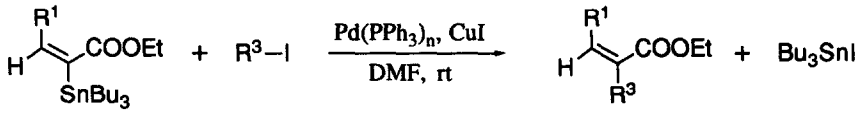
7: R^1 = alkyl, aryl; R^2 = H; R^3 = (hetero)aryl, alkenyl



(*E*)-**2**: R^1 = alkyl, aryl; R^2 = H

Thus, we explored the possibility of using a similar protocol for the direct synthesis of 2-(hetero)aryl and 2-(1-alkenyl) substituted ethyl 2-alkenoates, **7** (R^1 = alkyl, (hetero)aryl; R^2 = H; R^3 = aryl, alkenyl) from stannylesters (*E*)-**2** (R^1 = alkyl, aryl; R^2 = H) and in a preliminary test (entry 1, Table 1) we found that, when ethyl (*E*)-2-tributylstannyl-2-heptenoate, (*E*)-**2a**, was reacted with 0.4 equiv of iodobenzene, **11a**, in DMF at room temperature for 24 h, in the presence of 10 mol % of $Pd(PPh_3)_4$ and 0.75 equiv of CuI, pure ethyl (*Z*)-2-phenyl-2-heptenoate, (*Z*)-**7a** was obtained in 87 % yield.

Table 1. Palladium(0)/Copper(I)-Mediated Cross-Coupling Reaction between Alkyl (*E*)-2-Tributylstannyl-2-alkenoates and (Hetero)Aryl or Alkenyl Iodides[a].



(*E*)-**2** **11** **7** **12**

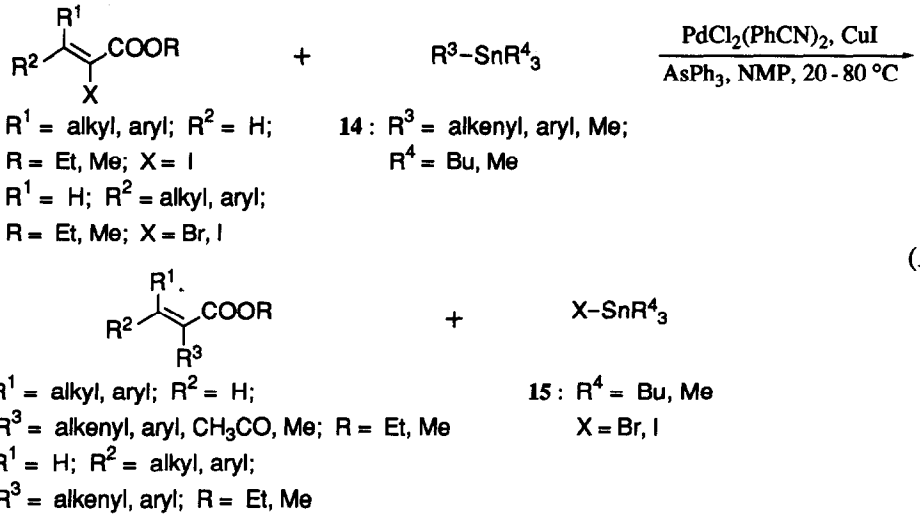
(R^1 = alkyl, aryl; R^3 = aryl, alkenyl)

Entry	Organostannane (*E*)-**2**		Organic iodide **11**		Palladium Catalyst	Reaction time (h)	Product **7**	Yield (%)
	Compd.	R^1	Compd.	R^3				
1[b]	(*E*)-**2a**	*n*-C_4H_9	**11a**	C_6H_5	$Pd(PPh_3)_4$	24	(*Z*)-**7a**	87
2	(*E*)-**2a**	*n*-C_4H_9	**11a**	C_6H_5	$Pd(PPh_3)_4$	30	(*Z*)-**7a**	77
3	(*E*)-**2a**	*n*-C_4H_9	**11b**	EtOOC-CH=CH (*E*)	$Pd(PPh_3)_4$	7	(*Z*,*E*)-**7b**	66
4	(*E*)-**2b**	C_6H_5	**11a**	C_6H_5	$Pd(PPh_3)_n$[c]	72	(*Z*)-**7c**	75
5	(*E*)-**2b**	C_6H_5	**11c**	2-thienyl	$Pd(PPh_3)_n$[c]	23	(*E*)-**7d**	79

[a] These reactions unless otherwise reported were performed in DMF at room temperature, in the presence of 10 mol % of the Pd(0) compound and 0.75 equiv of CuI, using a 1:1 molar ratio between (*E*)-**2** and **11**. [b] This reaction was carried out using a 2.5 molar ratio between (*E*)-**2** and **11**. [c] This palladium(0) catalyst was prepared *in situ* by reaction of $Pd(OAc)_2$ with 3 equiv of PPh_3 in DMF at 50 °C for 1 h.

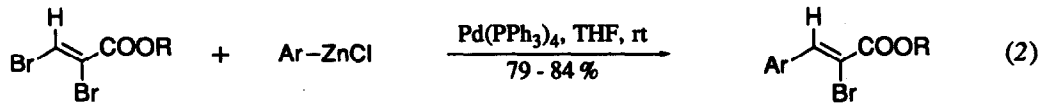
We were also gratified to find that the cross-coupling reaction between (*E*)-**2a** and **11a** could successfully be performed with the use of a 1 : 1 molar ratio between these reagents (entry 2, Table 1). In fact, the isolated yield was still satisfactory (77 %). Thus, the subsequent experiments (entries 3-5, Table 1) were carried out using a 1 : 1 molar ratio between organostannanes (*E*)-**2** and (hetero)aryl or alkenyl iodides. In this way ethyl (*Z*)-2-[(*E*)-2-ethoxycarbonylethenyl]-2-heptenoate, (*Z,E*)-**7b**, was prepared in 66 % yield from (*E*)-**2a** and ethyl (*E*)-3-iodopropenoate, **11b** (entry 3, Table 1). Interestingly, the cross-coupling reaction between compounds (*E*)-**2** and (hetero)aryl iodides could more conveniently be carried out using 10 mol % of a zerovalent palladium catalyst prepared *in situ* from $Pd(OAc)_2$ and 3 equiv of PPh_3[5] instead of pure $Pd(PPh_3)_4$, along with 0.75 equiv of CuI (entries 4 and 5, Table 1). Under these experimental conditions ethyl (*Z*)-2,3-diphenylpropenoate, (*Z*)-**7c**, and ethyl (*E*)-3-phenyl-2-(2-thienyl)propenoate, (*E*)-**7d**, were synthetized in 75 and 79 % yields, respectively.

Despite these satisfactory results, we thought it right to develop a more general procedure for the selective synthesis of stereodefined trisubstituted α,β-unsaturated esters of general formula **7**. This procedure, which was based on the palladium/copper-mediated cross-coupling reaction between organostannanes and stereoisomerically pure (*E*)- or (*Z*)-2-halo-2-alkenoates, allowed to prepare stereospecifically several variously 2-substituted alkyl (*Z*)- and (*E*)-2-alkenoates, respectively [(eqn 1)].



(*1*)

Alkyl (*E*)-2-iodo-2-alkenoates, (*E*)-**3**, used in these coupling reactions were synthetized in high yields by iododestannylation of the corresponding alkyl (*E*)-2-tributylstannyl-2-alkenoates[2]. Ethyl (*Z*)-2-iodo-2-heptenoate, (*Z*)-**13a**, was prepared in 73 % yield by reaction of ethyl propiolate with lithium dibutylcuprate in Et_2O at -78 C, followed by treatment with iodine[6], but an attempt to prepare (*Z*)-2-iodo-2-arylpropenoates according to a similar procedure failed. Thus, in the above mentioned cross-coupling reactions we used stereoisomerically pure ethyl (*Z*)-2-bromo-3-arylpropenoates, (*Z*)-**13** (R^1 = H; R^2 = aryl; X = Br), which were selectively synthetized in high yields by reaction of ethyl (*Z*)-2,3-dibromopropenoates, (*Z*)-**6**, with 1.2 equiv of arylzinc chlorides in THF at room temperature, in the presence of 5 mol % of $Pd(PPh_3)_4$[3] [(eqn 2)].



(Z)-**6a** : R = Et **16a** : Ar = C_6H_5 (Z)-**13b** : Ar = C_6H_5, R = Et

(Z)-**6b** : R = Me **16b** : Ar = 4-F-C_6H_4 (Z)-**13e** : Ar = 4-F-C_6H_4, R = Me

As shown in eqn 1 and Table 2, the reaction conditions recently employed for alkenylation and arylation of 2-iodo-2-cycloalkenones[7] or methylation and vinylation of stereodefined 2-iodo-2-alkenones[8] proved to be suitable for the coupling of our substrates with a variety of organotin derivatives. The results of several cross-coupling reactions of vinyltributylstannane, **14a**, (1-ethoxyvinyl)tributylstannane, **14b**, (*E*)-2-methyl-1-octenyltrimethylstannane, **14c**[9], (*Z*)-3-acetoxy-1-propenyltributylstannane, **14d**[10], ethyl (*Z*)-3-trimethylstannylpropenoate, **14e**[11], allyltributylstannane, **14f**, tetramethylstannane, **14g**, and phenyltrimethylstannane, **14h**, with stereodefined alkyl 2-halo-2-alkenoates, which were prepared according to the above mentioned procedures, are summarized in Table 2.

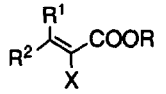
Some aspects of these results merit comments. Firstly, all reactions involving compounds **14a** and **14c** as well as that between **14g** and (*E*)-**3b** (entries 1, 3, 4, 6-8, 10 and 12, Table 2) were quite efficient, but those between compounds **14b** and (*E*)-**3a**, **14d** and (*E*)-**3c**, **14e** and (*E*)-**3b**, **14g** and (*E*)-**3c** as well as those of **14h** with (*Z*)-**13e** and (*E*)-**3b** were sluggish and required long reaction times and/or reaction temperatures higher than 20 °C (entries 2, 5, 9, 13-15, Table 2). On the other hand, disappointingly, the reaction between (*E*)-**3b** and **14f** failed to produce the desired cross-coupled product (entry 11, Table 2). Secondly, as expected, the two stereoisomers of an alkyl 2-halo-2-alkenoate exhibited quite different reactivity toward a same organotin derivative. Thus, even though the reactions of (*Z*)-**13a** and (*E*)-**3a** with **14a** gave comparable yields, the coupling of (*Z*)-**13a** with **14a** was quite slower than that between (*E*)-**3a** and **14a** (entries 1 and 8 , Table 2). Thirdly, all successful reactions proceeded with clean retention of stereochemistry. Therefore, these results contrast with those obtained either in the cross-coupling reactions of compounds (*E*)-**3** with alkenylzinc chlorides or methylzinc chloride in the presence of catalytic amounts of $Pd(PPh_3)_4$[2], or in the palladium/copper-mediated reactions between (*E*)-2-iodo-2-alkenones and organotin derivatives[8]. Finally, it must be noted that the reaction of (*E*)-**3a** and **14b** followed by an acidic work-up of the crude reaction product allowed the direct preparation of ethyl (*Z*)-2-acetyl-2-heptenoate, (*Z*)-**7f**, in a satisfactory yield (entry 2, Table 2).

B) Synthesis of (Z)- and (E)-α-ylidene-γ-butyrolactones

The fact that stereoisomerically pure alkyl 2-ethenyl-2-alkenoates (*Z*)-**7e**, (*Z*)-**7g**, (*Z*)-**7j**, (*Z*)-**7k**, (*E*)-**7e** and (*E*)-**7g** could be obtained in high yields (69-85 %) in the above mentioned cross-coupling reactions promted us to explore the possibility of using such compounds as precursors to (*Z*)- and (*E*)-α-ylidene-γ-butyrolactones, (*Z*)- and (*E*)-**8**, a class of substances which has been the subject of extensive research since they serve as useful intermediates in organic synthesis[12] and possess structural features widely distributed in nature[13]. Thus, a variety of methods have been reported in the literature for their stereocontrolled synthesis[14].

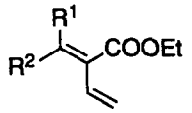
The simple and quite efficient new procedure which we developed for the stereocontrolled synthesis of compounds (*Z*)- and (*E*)-**8**, consisted in the selective reaction of alkyl (*Z*)- and (*E*)-2-ethenyl-2-alkenoates

Table 2. Palladium(0)/Copper(I)-Mediated Reactions between Stereodefined Alkyl 2-Halo-2-alkenoates and Organostannanes[a].

Entry	Alkyl 2-halo-2-alkenoate (*E*)-**3** or (*Z*)-**13** 					Organostannane **14** R^3-SnR^4_3			Reactions conditons (h/°C)	Product **7**	Isolated yield (%)
	Compd.	R^1	R^2	X	R	Compd.	R^3	R^4			
1	(*E*)-**3a**	*n*-C_4H_9	H	I	Et	**14a**	CH_2=CH	Bu	2.5 / 20	(*Z*)-**7e**	83
2	(*E*)-**3a**	*n*-C_4H_9	H	I	Et	**14b**	CH_2=C(OEt)	Bu	22 / 20 - 2 / 40	(*Z*)-**7f** [b]	47
3	(*E*)-**3b**	C_6H_5	H	I	Et	**14a**	CH_2=CH	Bu	2.5 / 20	(*Z*)-**7g**	84
4	(*E*)-**3b**	C_6H_5	H	I	Et	**14c**	(*E*)-$C_6H_{13}(CH_3)$C=CH	Me	23 / 20	(*Z*,*E*)-**7h**	84
5	(*E*)-**3c**	*n*-C_5H_{11}	H	I	Me	**14d**	(*Z*)-$AcOCH_2$-CH=CH	Bu	64.5 / 20	(*Z*,*Z*)-**7i**	40
6	(*E*)-**3c**	*n*-C_5H_{11}	H	I	Me	**14a**	CH_2=CH	Bu	3 / 20	(*Z*)-**7j**	69
7	(*E*)-**3d**	$TBDMSO(CH_2)_3$	H	I	Et	**14a**	CH_2=CH	Bu	3 / 20	(*Z*)-**7k**	82
8	(*Z*)-**13a**	H	*n*-C_4H_9	I	Et	**14a**	CH_2=CH	Bu	23 / 20	(*E*)-**7e**	80
9	(*E*)-**3b**	C_6H_5	H	I	Et	**14e**	(*Z*)-EtOOC-CH=CH	Me	48 / 20	(*Z*,*Z*)-**7l**	30
10	(*Z*)-**13b**	H	C_6H_5	Br	Et	**14a**	CH_2=CH	Bu	29.5 / 20	(*E*)-**7g**	85
11	(*E*)-**3b**	C_6H_5	H	I	Et	**14f**	CH_2=CH-CH_2	Bu	72 / 55 - 168 / 80	—	—
12	(*E*)-**3b**	C_6H_5	H	I	Et	**14g**	Me	Me	16 / 80	(*Z*)-**7m**	91
13	(*E*)-**3c**	*n*-C_5H_{11}	H	I	Me	**14g**	Me	Me	24 / 80	(*Z*)-**7n**	38 [c]
14	(*Z*)-**13e**	H	4-FC_6H_4	Br	Me	**14h**	Ph	Me	3.5 / 50	(*E*)-**7o**	66
15	(*E*)-**3b**	C_6H_5	H	I	Et	**14h**	Ph	Me	6 / 20 - 14 / 50	(*Z*)-**7c**	52

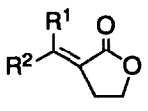
[a] These reactions were performed in the presence of 5 mol % of the $PdCl_2(PhCN)_2$, 10 mol % of CuI and 10 mol % of $AsPh_3$. The reactions involving **14g** were carried out using a 3:1 molar ratio between this reagent and the alkyl 2-halo-2-alkenoate, but those involving other organostannanes were performed using a 1.2 : 1 molar ratio between these organometallics and the alkyl 2-halo-2-alkenoates. [b] Ethyl (*Z*)-2-acetyl-2-heptenoate, (*Z*)-**7f**, was obtained by treatment of the crude reaction product derived from the coupling reaction with 0.6 N HCl at room temperature (see: Experimental). [c] GLC yield.

with a molar excess of dicyclohexylborane in THF at room temperature for 2.5 h followed by oxidation of the resultant organodicyclohexylborane with 30 % hydrogen peroxide in the presence of 3 N NaOH and lactonization of the crude reaction product, dissolved in benzene, by azeotropic distillation in the presence of a catalytic amount of *p*-toluenesulfonic acid [(eqn 3)].



(*Z*)-**7e**: $R^1 = C_4H_9$; $R^2 = H$
(*E*)-**7e**: $R^1 = H$; $R^2 = C_4H_9$
(*Z*)-**7g**: $R^1 = C_6H_5$; $R^2 = H$
(*E*)-**7g**: $R^1 = H$; $R^2 = C_6H_5$

1) $(c\text{-}C_6H_{11})_2BH$, THF
2) H_2O_2, NaOH
3) - cyclohexanol, + H_3O^+
4) p-TsOH, C_6H_6



(*Z*)-**8a**: $R^1 = C_4H_9$; $R^2 = H$
(*E*)-**8a**: $R^1 = H$; $R^2 = C_4H_9$
(*Z*)-**8b**: $R^1 = C_6H_5$; $R^2 = H$
(*E*)-**8b**: $R^1 = H$; $R^2 = C_6H_5$

(*3*)

In this way compounds (*Z*)-**8a**, (*E*)-**8a**, (*Z*)-**8b** and (*E*)-**8b** were synthetized in 62, 59, 62 and 65 % overall yields starting from (*Z*)-**7e**, (*E*)-**7e**, (*Z*)-**7g** and (*E*)-**7g**, respectively. It is interesting to note that compound (*E*)-**8b** is of importance as a fungicide and plant-growth regulator[15].

EXPERIMENTAL

All boiling and melting points are uncorrected. Precoated plastic sheets silica gel Merk 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m × 0.25 mm i.d.) and a AT-35 bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^1H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard.

All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive solutions were transferred with hypodermic syringes or double ended needles. Solvents were dried and distilled before use.

The following compounds were prepared according to the literature: $Pd(PPh_3)_4$[16], $PdCl_2(PhCN)_2$[17], 5-*tert*-butyldimethylsilyloxy-1-pentyne[18], ethyl (*E*)-3-phenyl-2-tributylstannylpropenoate, (*E*)-**2b**[2], methyl (*E*)-2-iodo-2-octenoate, (*E*)-**3c**[2], ethyl (*E*)-2-iodo-3-phenylpropenoate, (*E*)-**3b**[2], ethyl (*Z*)-2-iodo-2-heptenoate, (*Z*)-**13a**[6], ethyl (*E*)-3-iodopropenoate, (*E*)-**11b**[19], (*E*)-2-methyl-1-octenyltrimethylstannane, (*E*)-**14c**[9], (*Z*)-3-acetoxy-1-propenyltributylstannane, (*Z*)-**14d**[10] and ethyl (*Z*)-3-trimethylstannylpropenoate, (*Z*)-**14e**[11]. Ethyl 2-heptynoate (b.p. 78 - 79 °C/4 Torr; lit[20] b.p. 97.5 °C/16 Torr) was prepared in 66 % yield by treatment of a THF solution of 1-hexyne with 1 equiv of a 1.85 M Et_2O solution of methyllithium at -78 °C for 3 h and at -20 °C for 1 h, followed by addition of 1.1 equiv of ethyl chloroformate. Ethyl 6-(*tert*-butyldimethylsilyloxy)-2-hexynoate (b.p. 96 °C/0.2 Torr; lit[21] b.p. 105 - 115 °C/0.3 Torr) was prepared in 78 % yield using a similar procedure.

Ethyl (E)-2-tributylstannyl-2-heptenoate, (E)-2a

A degassed solution of Bu_3SnH (46.2 g, 0.159 mol) in dry THF (220 ml) was added during 1.5 h to a solution of ethyl 2-heptynoate (24.5 g, 0.159 mol) and $Pd(PPh_3)_4$ (3.67 g, 3.17 mmol) in dry THF (200 ml), which was stirred under argon at 20 °C. After 4 h an aliquot of the reaction mixture was removed by syringe for GLC analysis. Evidence for complete reaction was the absence of ethyl 2-heptynoate. THF was removed under reduced pressure and the residue was diluted with hexane (800 ml). After 1 h the precipitated Pd catalyst and PPh_3 were removed by filtration over Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with hexane (400 ml), filtered over Celite and concentrated *in vacuo*. GLC analysis of the residue showed the presence of two compounds in a *ca.* 90 : 10 molar ratio. This residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (99 : 1 *v/v*) as eluant, to give (*E*)-**2a** as an oil (67.4 g, 95 % yield). ^1H NMR ($CDCl_3$), δ: 6.04 (1H, t, J = 7.1 Hz, $^3J_{Sn\text{-}H}$ = 70 Hz, H-3), 4.15 (2H, q, J = 7.1 Hz, OCH_2), 2.41 (2H, *pseudo*-q, J = 7.1 Hz, H-4), 1.65 - 1.15 (19H, m, O-C-CH_3, H-5, H-6, H-2', and H-3'), 1.05 - 0.65 ppm (18H, m, H-7, H-1' and H-4'). MS, *m/z* (%): 389 (37), 388 (16), 387 (30), 343 (19), 179 (29), 177 (31), 165 (20), 57 (66), 41 (100), 40 (21), 30 (82), 28 (26). Anal. Calcd for $C_{21}H_{42}O_2Sn$: C, 56.65; H, 9.51. Found: C, 57.04; H, 10.13. GLC/MS and ^1H NMR analyses showed that (*E*)-**2a** was stereoisomerically pure but contaminated by less than 7 % of ethyl (*E*)-3-tributylstannyl-2-heptenoate. This compound had MS, *m/z* (%): 389 (100), 388 (59), 387 (82), 386 (41), 385 (48), 333 (39), 277 (38), 276 (29), 179 (30), 177 (36), 57 (30), 30 (64). ^1H NMR ($CDCl_3$), δ: 5.90 (1H, s, H-2).

Ethyl (E)-2-iodo-2-heptenoate, (E)-3a

A solution of iodine (22.8 g, 89.9 mmol) in dry CH_2Cl_2 (1020 ml) was added during 6 h to a solution of compound (*E*)-**2a** (40.0 g, 89.9 mmol) in dry CH_2Cl_2 (450 ml), which was stirred at 20 °C under argon. Upon completion of addition the reaction mixture was stirred for additional 2 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 ml) and stirred with a 50 % aqueous KF solution (300 ml) at room temperature for 2.5 h. The reaction mixture was filtered and the filtrate was extracted with Et_2O. The organic extract was dried and concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (90 : 10 *v/v*) as eluant, to give stereoisomerically pure (*E*)-**3a** (16.6 g, 65 % yield). ^1H NMR ($CDCl_3$), δ: 6.89 (1H, t, J = 7.3 Hz, H-3), 4.25 (2H, J = 7.1 Hz, OCH_2), 2.46 (2H, *pseudo*-q, J = 7.3 Hz, H-4), 1.53 - 1.23 (7H, m, H-5, H-6 and O-C-CH_3), 0.90 ppm (3H, t, J = 6.8 Hz, H-7). MS, *m/z* (%): 282 (26), 225 (22), 199 (18), 181 (11), 127 (17), 109 (17), 84 (10), 81 (36), 79 (11), 43 (43), 41 (58), 30 (100). Anal. Calcd for $C_9H_{15}IO_2$: C, 38.31; H, 5.36. Found : 37.99; H, 5.24. GLC showed that (*E*)-**3a** had 97 % chemical purity.

General procedure for the palladium/copper-mediated reaction between alkyl (E)-2-tributylstannyl-2-alkenoates, (E)-2, and aryl or alkenyl iodides

In a typical experiment to a degassed solution of an organic iodide (6.74 mmol) in DMF (67 ml) were sequentially added compound (*E*)-**2** (6.74 mmol) and $Pd(PPh_3)_4$ (0.78 g, 0.67 mmol). Copper(I) iodide (0.96 g, 5.05 mmol) was then added in one portion and the resulting mixture was stirred under argon at room temperature for the period of time reported in Table 1. After completion of the reaction, which was periodically monitored by GLC analysis, the reaction mixture was diluted with Et_2O and filtered over Celite. The filtrate

was stirred for 1 h with a large excess of a saturated aqueous NH_4Cl solution and the resultant organic phase was separated. It was then washed with brine, dried and concentrated *in vacuo*. The residue was diluted with Et_2O (100 ml), stirred for 3 h with an excess of a 50 % aqueous KF solution, filtered over Celite and the filtrate was repeatedly extracted with Et_2O. The collected organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel. Ethyl (*Z*)-2-phenyl-2-heptenoate, (*Z*)-**7a**, and ethyl (*Z*)-2-[(*E*)-2-ethoxycarbonylethenyl]-2-heptenoate, (*Z,E*)-**7b** (entries 2 and 3, Table 1) were prepared according to this procedure. On the other hand, ethyl (*Z*)-2,3-diphenylpropenoate, (*Z*)-**7c** and ethyl (*E*)-3-phenyl-2-(2-thienyl)propenoate, (*E*)-**7d** (entries 4 and 5, Table 1) were prepared according to the following modification of the above mentioned procedure. A dried flask flushed with argon was charged with $Pd(OAc)_2$ (0.178 g, 0.793 mmol), PPh_3 (0.624 g, 2.38 mmol) and DMF (70 ml) and the mixture was stirred at 50 °C for 1 h. The solution of $Pd(PPh_3)_n$ species so obtained[5] was cooled to room temperature and copper(I) iodide (1.13 g, 5.95 mmol) and a mixture of compound (*E*)-**2** (7.93 mmol) and the organic iodide (7.93 mmol) diluted with DMF (10 ml) were sequentially added. The resulting mixture was stirred under argon for the period of time reported in Table 1 and worked up as described above.

Ethyl (Z)-2-phenyl-2-heptenoate, (Z)-7a

The crude reaction mixture, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**2a** and iodobenzene, **11a** (entry 2, Table 1), was purified by MPLC on silica gel, using a mixture of hexane and benzene (70 : 30 *v/v*) as eluant, to give (*Z*)-**2a** as an oil (77 % yield). ^1H NMR ($CDCl_3$), δ: 7.45 - 7.16 (5H, m, C_6H_5), 6.17 (1H, t, J = 7.6 Hz, H-3), 4.29 (2H, q, J = 7.2 Hz, OCH_2), 2.42 (2H, *pseudo*-q, J = 7.6 Hz, H-4), 1.62 - 1.28 (4H, m, H-5 and H-6), 1.32 (3H, t, J = 7.2 Hz, O-C-CH_3), 0.93 ppm (3H, t, J = 7.3 Hz, H-7). MS, *m/z* (%): 232 (45), 157 (40), 148 (21), 129 (28), 117 (27), 115 (80), 91 (26), 43 (43), 41 (57), 40 (21), 30 (100), 28 (61). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.56; H, 8.76. GLC analysis showed that (*Z*)-**7a** had chemical purity higher than 97 %.

When (*E*)-**2a** was reacted with 0.4 equiv of **11a** in DMF at room temperature for 24 h using the same catalyst system, compound (*Z*)-**7a** was isolated in 87 % yield (entry 1, Table 1).

Ethyl (Z)-2-[(E)-2-ethoxycarbonylethenyl]-2-heptenoate, (Z,E)-7b

The crude reaction mixture, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**2a** and ethyl (*E*)-3-iodopropenoate, **11b** (entry 3, Table 1), was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (93 : 7 *v/v*) as eluant, to give (*Z,E*)-**7b** as an oil in 66 % yield. The spectral properties of this stereoisomerically pure compound were in very good agreement with those previously reported[6].

Ethyl (Z)-2,3-diphenylpropenoate, (Z)-7c

The crude reaction mixture, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**2b** and **11a** (entry 4, Table 1), was purified by MPLC on silica gel, using a mixture of hexane and benzene (55 : 45 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**7c** as an oil in 75 % yield. The spectral properties of this compound were in very good agreement with those previously reported[2].

This compound was also prepared in 52 % yield by Pd/Cu-mediated reaction between ethyl (*E*)-2-iodo-3-phenylpropenoate, (*E*)-**3b**, and phenyltrimethylstannane, **14h** (entry 15, Table 2).

Ethyl (E)-3-phenyl-2-(2-thienyl]propenoate, (E)-7d

The crude reaction mixture, which was obtained from the Pd/Cu mediated reaction between (*E*)-**2b** and 2-iodothiophene, **11c** (entry 5, Table 1), was purified by MPLC on silica gel, using a mixture of hexane and benzene (50 : 50 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**7d** as an oil in 79 % yield. The spectral properties of this compound were in very good agreement with those previously reported[2].

Ethyl (E)-2-iodo-6-(tert-butyldimethylsilyloxy)-2-hexenoate, (E)-3d

A degassed solution of Bu_3SnH (14.12 g, 48.5 mmol) in dry THF (70 ml) was added during 50 min to a solution of ethyl 6-*tert*-butyldimethylsilyloxy-2-hexynoate (13.52 g, 50.0 mmol) and $Pd(PPh_3)_4$ (1.17 g, 1.01 mmol) in dry THF (70 ml), which was stirred under argon at room temperature. After 4 h the reaction mixture was concentrated *in vacuo* and the residue was diluted with hexane (600 ml). The resulting mixture was filtered over Celite and the filtrate was concentrated *in vacuo*. The residue was diluted with hexane (300 ml) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was diluted with dry CH_2Cl_2 (240 ml). A solution of iodine (12.31 g, 48.5 mmol) in dry CH_2Cl_2 (550 ml) was added dropwise to this solution, which was stirred at room temperature for additional 2 h after completion of the addition. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in Et_2O (460 ml) and stirred with a 50 % aqueous KF solution (460 ml) for 2 h at room temperature. The mixture was filtered over Celite and the filtrate was extracted with Et_2O. The organic extract was washed with a diluted aqueous $Na_2S_2O_3$ solution and water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (97 : 3 *v/v*) as eluant. Concentration of the intermediate chromatographic fractions allowed to obtain stereoisomerically pure (*E*)-**3d** as an oil (10.80 g, 56 % yield), which had chemical purity higher than 97 %. Concentration of the first and the last eluted chromatographic fractions allowed to obtain (*E*)-**3d** (5.17 g) having chemical purity higher than 87 %, which was subsequently purified by a second MPLC on silica gel. Compound (*E*)-**3d** had ^1H NMR ($CDCl_3$), δ: 5.94 (1H, t, J = 8.2 Hz, H-3), 4.24 (2H, q, J = 7.1 Hz, OCH_2), 3.63 (2H, t, J = 6.1 Hz, H-6), 2.53 (2H, *pseudo*-q, J = 8.2 Hz, H-4), 1.77 - 1.56 (2H, m, H-5), 1.32 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.04 ppm (6H, s, $SiMe_2$). Anal. Calcd for $C_{14}H_{27}IO_3Si$: C, 42.21; H, 6.83. Found: C, 42.49; H, 6.75.

Ethyl (Z)-2-bromo-3-phenylpropenoate, (Z)-13b

A 0.62 M THF solution of phenylmagnesium bromide (58.5 ml, 36.0 mmol) was added to a stirred solution of anhydrous $ZnCl_2$ (6.38 g, 46.8 mmol) in dry THF (50 ml), which was maintained at 0 °C. After stirring for 15 min at this temperature, $Pd(PPh_3)_4$ (1.73 g, 1.50 mmol) and ethyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**6a** (7.74 g, 30.0 mmol), which was prepared in 83 % yield by reaction between ethyl propiolate and 1.1 equiv of bromine in CCl_4 at 70 °C for 1.5 h[3, 22], were sequentially added and the resulting reaction mixture was stirred for 25 h at room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution cooled to 0 °C and extracted with Et_2O. The organic extract was washed with water, dried and concentrated *in vacuo*. The residue was dissolved in hexane (400 ml) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (70 : 30 *v/v*) as eluant, to give chemically and stereoisomerically pure (*Z*)-**13b** as an oil (6.04 g, 79 % yield). ^1H NMR ($CDCl_3$), δ: 8.22 (1H, s, H-3), 7.98 - 7.72 (2H, m, H_{orto}), 7.56 - 7.26 (3H, m, H_{meta} and H_{para}), 4.35 (2H, q, J = 7.1 Hz, OCH_2), 1.39 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). ^1H NMR (CCl_4): δ

8.13 (1H, s, H-3), 7.95 - 7.65 (2H, m, H_{orto}), 7.50 - 7.24 (3H, m, H_{meta} and H_{para}), 4.29 (2H, q, J = 7.1 Hz, OCH_2), 1.39 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 256 (17), 254 (18), 209 (10), 175 (56), 147 (99), 129 (25), 103 (24), 102 (100), 77 (21), 76 (30), 75 (22), 51 (28). The ^{1}H NMR spectrum of (*Z*)-**13b** registered in CCl_4 solution was in quite good agreement with that reported in the literature[23].

Methyl (Z)-2-bromo-3-(4-fluorophenyl)propenoate, (Z)-13e

A 0.83 M THF solution of 4-fluorophenylmagnesium bromide (36.2 ml, 30.0 mmol) was added to a stirred solution of anhydrous $ZnCl_2$ (5.32 g, 39.0 mmol) in dry THF (50 ml), which was maintained at 0 °C. After stirring for 15 min at this temperature, $Pd(PPh_3)_4$ (1.44 g, 1.25 mmol) and methyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**6b**[3] (6.10 g, 25.0 mmol) were sequentially added. The resulting reaction mixture was stirred at room temperature for 23 h and then worked up according to the procedure used for the preparation of (*Z*)-**13b**. The crude reaction product was purified by MPLC on silica gel, using a mixture of hexane and benzene (80 : 20 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**13e** (5.47 g, 84 % yield): m.p. 45 °C. ^{1}H NMR ($CDCl_3$), δ: 8.19 (1H, s, H-3), 7.88 (2H, dd, J = 8.8 and 5.4 Hz, H_{orto}), 7.12 (2H, *pseudo*-t, J = 8.8 Hz, H_{meta}), 3.90 ppm (3H, s, OCH_3). MS, *m/z* (%): 260 (14), 258 (15), 180 (12), 179 (100), 147 (50), 120 (66), 99 (7), 94 (11), 74 (7), 59 (16), 30 (19). Anal. Calcd for $C_{10}H_{18}BrFO_2$: C, 46.36; H, 3.11. Found: C, 46.06; H, 3.29.

General procedure for the palladium/copper-mediated cross-coupling reactions of alkyl 2-halo-2-alkenoates, (E)-3 and (Z)-13, with organostannanes, 14

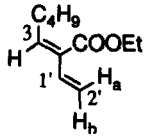
A dried flask flushed with argon was charged with $PdCl_2(PhCN)_2$ (0.43 g, 1.13 mmol), CuI (0.43 g, 2.25 mmol), $AsPh_3$ (0.69 g, 2.25 mmol) and a solution of a stereodefined 2-halo-2-alkenoate, (*E*)-**3** or (*Z*)-**13** (22.5 mmol) in N-methylpyrrolidinone (NMP) (23 ml). A degassed organostannane **14** was then added and the mixture was stirred at the temperature and for the period of time reported in Table 2. The reactions involving tetramethylstannane, **14g** (entries 12 and 13, Table 2) were carried out using a 3 : 1 molar ratio between such organometallic reagent and the alkyl-2-halo-2-alkenoate, but the coupling reactions involving other organostannanes were performed using a 1.2 : 1 molar ratio between such organometallics and the organic electrophiles. After completion of the reaction, which was periodically monitored by GLC and/or TLC analyses, the reaction mixture was cooled to room temperature and poured into a large excess of a saturated aqueous NH_4Cl solution. After stirring for 0.5 h in the air the mixture was repeatedly extracted with Et_2O. The crude Et_2O extracts derived from the reactions involving organotributylstannanes were stirred for 2 - 3 h with a large excess of a 50 % aqueous KF solution, filtered over Celite and the filtrates were repeatedly extracted with Et_2O. The collected organic extracts were washed with brine, dried, filtered, concentrated under reduced pressure and the residue was analyzed by GLC/MS and TLC. It was then diluted with the solvent mixture used in TLC analysis as the eluant and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel using the same eluant employed for the TLC analysis.

Compounds **7e-7o** and **7c** were prepared according to this procedure (Table 2).

Ethyl (Z)-2-ethenyl-2-heptenoate, (Z)-7e

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between ethyl (*E*)-2-iodo-2-heptenoate, (*E*)-**3a**, and vinyltributylstannane, **14a** (entry 1, Table 2), was purified by MPLC on

silica gel, using a mixture of hexane and benzene (75 : 25 *v/v*) as eluant, to give (*Z*)-**7e** as an oil in 83 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 6.33 (1H, dd, *J* = 17.5 and 10.9 Hz, H-1'), 5.92 (1H, t, *J* = 7.6 Hz, H-3), 5.25 (1H, d, *J* = 17.5 Hz, H-2'$_a$), 5.08 (1H, d, *J* = 10.9 Hz, H-2'$_b$), 4.29 (2H, q, *J* = 7.1 Hz, OCH_2), 2.29 (2H, *pseudo*-q, *J* = 7.6 Hz, H-4), 1.53 - 1.18 (4H, m, H-5 and H-6), 1.34 (3H, t, *J* = 7.1 Hz, O-C-CH_3), 0.90 ppm (3H, t, *J* = 7.1 Hz, H-7). MS, *m/z* (%): 182 (18), 137 (24), 107 (28), 81 (24), 79 (33), 67 (55), 55 (31), 53 (26), 43 (41), 41 (81), 40 (62), 30 (100). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found; C, 72.19; H, 9.94. GLC and ^{1}H NMR analyses showed that (*Z*)-**7e** had stereoisomeric purity higher than 99 %.



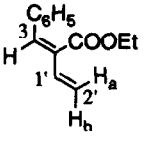
(*Z*)-**7e**

Ethyl (Z)-2-acetyl-2-heptenoate, (Z)-7f

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**3a** and (1-ethoxyethenyl)tributylstannane, **14b** (entry 2, Table 2), was dissolved in benzene (65 ml) and stirred for 12 h at room temperature in the presence of 0.6 N HCl (65 ml). The resulting reaction mixture was extracted thoroughly with benzene, washed with brine, dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give (*Z*)-**7f** as an oil in 47 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 6.85 (1H, t, *J* = 7.7 Hz, H-3), 4.32 (2H, q, *J* = 7.1 Hz, OCH_2), 2.33 (2H, *pseudo*-q, *J* = 7.7 Hz, H-4), 2.32 (3H, s, CH_3CO), 1.58 - 1.22 (4H, m, H-5 and H-6), 1.34 (3H, t, *J* = 7.1 Hz, O-C-CH_3), 0.92 ppm (3H, t, *J* = 7.1 Hz, H-7). MS, *m/z* (%): 198 (2), 167 (11), 152 (10), 137 (23), 123 (10), 81 (14), 53 (12), 43 (100), 41 (22), 40 (11), 30 (39), 28 (29). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.31. GLC analysis showed that (*Z*)-**7f** had stereoisomeric purity higher than 99 %.

Ethyl (Z)-2-ethenyl-3-phenylpropenoate, (Z)-7g

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between ethyl (*E*)-2-iodo-3-phenylpropenoate, (*E*)-**3b**, and **14a** (entry 3, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (55 : 45 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**7g** as an oil in 84 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 7.42 - 7.19 (5H, m, C_6H_5), 6.63 (1H, s, H-3), 6.46 (1H, dd, *J* = 17.5 and 10.7 Hz, H-1'), 5.33 (1H, d, *J* = 17.5 Hz, H-2'$_a$), 5.27 (1H, d, *J* = 10.7 Hz, H-2'$_b$), 4.27 (2H, q, *J* = 7.1 Hz, OCH_2), 1.21 ppm (3H, t, *J* = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 202 (12), 173 (10), 157 (12), 130 (11), 129 (100), 128 (44), 127 (18), 117 (8), 77 (8), 51 (36), 50 (10), 39 (18). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.10; H, 6.95.



(*Z*)-**7g**

Ethyl (Z)-3-phenyl-2-[(E)-2-methyl-1-octenyl]propenoate, (Z,E)-7h

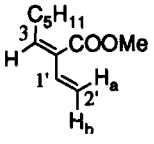
The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**3b** and (*E*)-2-methyl-1-octenyltrimethylstannane, (*E*)-**14c** (entry 4, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (80 : 20 *v/v*) as eluant, to give chemically and stereoisomerically pure (*Z,E*)-**7h** as an oil in 84 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 7.45 - 7.05 (5H, m, C_6H_5), 6.58 (1H, s, H-3), 5.90 (1H, *pseudo*-quint, *J* = 1.2 Hz, H-1'), 4.18 (2H, q, *J* = 7.2 Hz, OCH_2), 2.11 (2H, t, *J* = 6.8 Hz, H-3'), 1.77 (3H, d, *J* = 1.2 Hz, =C-CH_3), 1.44 - 1.18 (8H, br m, H-4', H-5', H-6' and H-7'), 1.16 (3H, t, *J* = 7.2 Hz, O-C-CH_3), 0.89 ppm (3H, t, *J* = 6.3 Hz, H-8'). MS, *m/z* (%): 300 (38), 229 (33), 183 (54), 169 (38), 155 (54), 143 (100), 141 (49), 129 (31), 115 (56), 91 (41), 55 (30), 43 (91). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.27; H, 9.81.

Methyl (Z)-2-[(Z)-3-acetoxy-1-propenyl]-2-octenoate, (Z,Z)-7i

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between methyl (*E*)-2-iodo-2-octenoate, (*E*)-**3c**, and (*Z*)-3-acetoxy-1-propenyltributylstannane, (*Z*)-**14d** (entry 5, Table 2), was purified by MPLC on silica gel, using benzene as eluant, to give stereoisomerically pure (*Z,Z*)-**7i** as an oil in 40 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 6.31 (1H, dd, *J* = 11.5 and 1.5 Hz, H-1'), 5.98 (1H, t, *J* = 7.5 Hz, H-3), 5.66 (1H, dt, *J* = 11.5 and 6.7 Hz, H-2'), 4.64 (2H, dd, *J* = 6.7 and 1.5 Hz, H-3'), 3.76 (3H, s, OCH_3), 2.52 (2H, *pseudo*-q, *J* = 7.5 Hz, H-4), 2.06 (3H, s, $COCH_3$), 1.55 - 1.20 (6H, m, H-5, H-6 and H-7), 0.90 ppm (3H, t, *J* = 6.5 Hz, H-8). MS, *m/z* (%): 254 (1), 180 (9), 137 (6), 105 (5), 93 (10), 91 (7), 79 (9), 59 (12), 55 (8), 53 (8), 43 (100), 41 (31). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.01; H, 8.67.

Methyl (Z)-2-ethenyl-2-octenoate, (Z)-7j

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**3c** and **14a** (entry 6, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (70 : 30 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**7j** as an oil in 69 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 6.34 (1H, dd, *J* = 17.5 and 10.9 Hz, H-1'), 5.96 (1H, t, *J* = 7.6 Hz, H-3), 5.24 (1H, d, *J* = 17.5 Hz, H-2'$_a$), 5.09 (1H, d, *J* = 10.9 Hz, H-2'$_b$), 3.81 (3H, s, OCH_3), 2.28 (2H, *pseudo*-q, *J* = 7.6 Hz, H-4), 1.52 - 1.14 (6H, m, H-5, H-6 and H-7), 0.89 ppm (3H, t, *J* = 6.4 Hz, H-8). MS, *m/z* (%): 182 (8), 113 (11), 81 (19), 79 (16), 67 (12), 59 (26), 55 (23), 53 (29), 45 (16), 43 (19), 42 (14), 41 (100). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.31; H, 10.26.

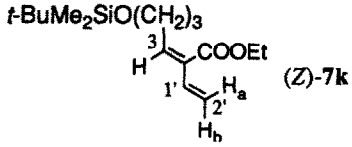


(Z)-**7j**

Ethyl (Z)-2-ethenyl-6-(tert-butyldimethylsilyloxy)-2-hexenoate, (Z)-7k

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between ethyl (*E*)-2-iodo-6-(*tert*-butyldimethylsilyloxy)-2-hexenoate, (*E*)-**3d**, and **14a** (entry 7, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (50 : 50 v/v) as eluant, to give 95 % stereoisomerically pure (*Z*)-**7k** as an oil in 82 % yield. ^{1}H NMR ($CDCl_3$), *δ*: 6.33 (1H, dd, *J* = 17.5 and 10.9 Hz, H-1'), 5.95

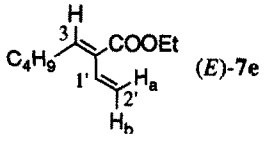
(1H, t, J = 7.5 Hz, H-3), 5.26 (1H, d, J = 17.5 Hz, H-2'$_a$), 5.09 (1H, d, J = 10.9 Hz, H-2'$_b$), 4.28 (2H, q, J = 7.5 Hz, H-4), 1.66 (2H, tt, J = 6.3 and 7.5 Hz, H-5), 1.34 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.04 ppm (6H, s, $SiMe_2$). MS, *m/z* (%): 298 (1), 241 (96), 121 (27), 103 (65), 93 (46), 91 (28), 77 (26), 75 (83), 73 (30), 59 (39), 57 (30), 45 (46), 41 (100). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.56; H, 10.17.



(*Z*)-**7k**

Ethyl (E)-2-ethenyl-2-heptenoate, (E)-7e

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between ethyl (*Z*)-2-iodo-2-heptenoate, (*Z*)-**13a**, and **14a** (entry 8, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (80 : 20 *v/v*) as eluant, to give stereoisomerically pure (*E*)-**7e** as an oil in 80 % yield. ^{1}H NMR ($CDCl_3$), δ: 6.73 (1H, t, J = 7.7 Hz, H-3), 6.48 (1H, dd, J = 17.7 and 11.5 Hz, H-1'), 5.57 (1H, d, J = 17.7 Hz, H-2'$_a$), 5.36 (1H, d, J = 11.5 Hz, H-2'$_b$), 4.23 (2H, q, J = 7.1 Hz, OCH_2), 2.32 (2H, *pseudo*-q, J = 7.7 Hz, H-4), 1.60 - 1.16 (4H, m, H-5 and H-6), 1.32 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.93 ppm (3H, t, J = 7.6 Hz, H-7). MS, *m/z* (%): 182 (18), 107 (29), 98 (27), 81 (28), 79 (34), 67 (64), 55 (27), 43 (36), 41 (77), 40 (43), 30 (100), 28 (70). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.71; H, 10.14.



(*E*)-**7e**

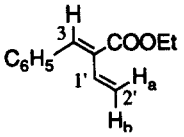
Ethyl (Z)-2-[(Z)-2-ethoxycarbonylethenyl]-3-phenylpropenoate, (Z,Z)-7l

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**3b** and ethyl (*Z*)-3-trimethylstannylpropenoate, **14e** (entry 9, Table 2), was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give stereoisomerically pure (*Z,Z*)-**7l** as an oil in 30 % yield. ^{1}H NMR ($CDCl_3$), δ: 7.68 - 7.64 (1H, m, H-3), 7.52 - 7.24 (5H, m, C_6H_5), 6.78 (1H, dd, J = 11.7 and 2.0 Hz, H-1'), 6.13 (1H, dd, J = 11.7 and 0.9 Hz, H-2'), 4.24 (2H, q, J = 7.1 Hz, OCH_2), 4.15 (2H, q, J = 7.1 Hz, OCH_2), 1.30 (3H, t, J = 7.1 Hz, O-C-CH_3), 1.26 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 274 (6), 201 (38), 200 (11), 173 (47), 172 (12), 155 (43), 129 (59), 128 (28), 127 (28), 117 (15), 115 (26), 102 (11), 29 (100). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61; H, 69.90; H, 6.88.

Ethyl (E)-2-ethenyl-3-phenylpropenoate, (E)-7g

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between ethyl (*Z*)-2-bromo-3-phenylpropenoate, (*Z*)-**13b**, and **14a** (entry 10, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (55 : 45 *v/v*) as eluant, to give stereoisomerically pure (*E*)-**7g** as an oil in 85 % yield. ^{1}H NMR ($CDCl_3$), δ: 7.54 (1H, s, H-3), 7.48 - 7.26 (5H, m, C_6H_5), 6.64 (1H, dd, J = 17.7 and 11.6 Hz, H-1'), 5.85 (1H, d, J = 17.7 Hz, H-2'$_a$), 5.43 (1H, d J = 11.6 Hz, H-2'$_b$), 4.31 (2H, q,

J = 7.2 Hz, OCH_2), 1.39 ppm (3H, t, J = 7.2 Hz, O-C-CH_3). MS, *m/z* (%): 202 (5), 129 (99), 128 (57), 127 (24), 102 (16), 77 (26), 63 (13), 51 (33), 43 (13), 40 (12), 30 (100), 28 (55). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.54; H, 7.12.



(*E*)-**7g**

Ethyl (Z)-2-methyl-3-phenylpropenoate, (Z)-7m

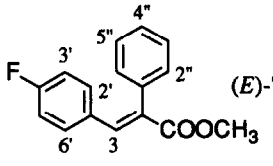
The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between (*E*)-**3b** and tetramethylstannane, **14g** (entry 12, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (55 : 45 *v/v*) as eluant, to give stereoisomerically pure (*Z*)-**7m** as an oil in 91 % yield. ^{1}H NMR ($CDCl_3$), δ: 7.40 - 7.10 (5H, m, C_6H_5), 6.70 (1H, q, J = 1.6 Hz, H-3), 4.11 (2H, q, J = 7.1 Hz, OCH_2), 2.09 (3H, d, J = 1.6 Hz, =C-CH_3), 1.10 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.39; H, 7.22.

Methyl (Z)-2-methyl-2-octenoate, (Z)-7n

This compound was obtained in 38 % GLC yield from the Pd/Cu-mediated reaction between (*E*)-**3c** and **14g** (entry 13, Table 2). Purification of the crude reaction mixture by MPLC on silica gel, using a mixture of hexane and benzene (75 : 25 *v/v*) as eluant, allowed to isolate a small sample of pure (*Z*)-**7n**. ^{1}H NMR ($CDCl_3$), δ: 5.94 (1H, dq, J = 7.4 and 1.5 Hz, H-3), 3.73 (1H, s, OCH_3), 2.45 (2H, *pseudo*-q, J = 7.4 Hz, H-4), 1.89 (3H, *pseudo*-q, J = 1.5 Hz, =C-CH_3), 1.50 - 1.10 ppm (9H, m, H-5, H-6, H-7 and H-8). MS, *m/z* (%): 170 (48), 139 (21), 129 (13), 127 (100), 115 (11), 101 (63), 95 (35), 84 (11), 81 (13), 67 (27), 55 (60). The spectral properties of this compound were in agreement with those previously reported[24].

Methyl (E)-3-(4-fluorophenyl)-2-phenylpropenoate, (E)-7o

The crude reaction product, which was obtained from the Pd/Cu-mediated reaction between methyl (*Z*)-2-bromo-3-(4-fluorophenyl)propenoate, (*Z*)-**13e**, and phenyltrimethylstannane, **14h** (entry 14, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and benzene (50 : 50 *v/v*) as eluant, to give stereoisomerically pure (*E*)-**7o** in 66 % yield. M.p. 66 - 67 °C. ^{1}H NMR ($CDCl_3$), δ: 7.81 (1H, s, H-3), 7.44 - 7.33 (3H, m, H-3", H-4", H-5"), 7.25 - 7.17 (2H, m, H-2", H-6"), 7.01 (2H, dd, J = 8.8 and 5.6 Hz, H-2' and H-6'), 6.84 (2H, *pseudo*-t, J = 8.8 Hz, H-3' and H-5'), 3.79 ppm (3H, s, OCH_2). MS, *m/z* (%): 256 (32), 197 (38), 196 (42), 194 (7), 177 (9), 170 (10), 140 (9), 139 (100), 59 (13), 51 (8). Anal. Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11. Found : C, 74.88; H, 5.28.



(*E*)-**7o**

General procedure for the synthesis of stereodefined α-ylidene-γ-butyrolactones, 8, from stereodefined alkyl 2-ethenyl-2-alkenoates

In a typical experiment, cyclohexene (4.16 g, 49.4 mmol) was added dropwise to a solution of borane-methylsulfide complex (2.34 ml, 24.7 mmol) in dry THF (17 ml), which was stirred under a nitrogen atmosphere at 0 °C. After completion of the addition the mixture was stirred for additional 1 h at 0 °C and then cooled to -15 °C. A solution of an alkyl 2-ethenyl-2-alkenoate (12.4 mmmol) in dry THF (25 ml) was added dropwise and the resulting mixture was stirred for 2.5 h at room temperature. After this period it was cooled to 0 °C and a mixture of water (0.22 ml, 12.4 mmol) and THF (2.2 ml) was added. The reaction mixture was then concentrated at 20 Torr and 0 °C and the residue was diluted with THF (50 ml). 3 N NaOH (20.6 ml, 61.8 mmol) was added followed by dropwise addition of 30 % H_2O_2 (7.5 ml, 74.2 mmol), maintaining the temperature below 40 °C. The resulting mixture was stirred for 0.5 h at 40 °C and then cooled to room temperature. Water was added and the mixture was extracted repeatedly with Et_2O. The collected organic extracts were washed with water until neutrality. The aqueous phase was cooled to 0 °C, acidified with 10 % H_2SO_4 and repeatedly extracted with Et_2O. The collected organic extracts were mixed with the previously obtained Et_2O extract, dried and concentrated *in vacuo*. *p*-Toluenesulfonic acid monohydrate (0.118 g, 0.62 mmol) was added to the residue diluted with benzene (60 ml). Azeotropic removal of water and/or ethanol yielded a crude benzene solution of the desired α-ylidene-γ-butyrolactone, **8**. This benzene solution was cooled to room temperature, diluted with Et_2O, washed with 5 % aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel. Compounds (*Z*)-**8a**, (*Z*)-**8b**, (*E*)-**8a** and (*E*)-**8b** were prepared according to this procedure.

(Z)-α-pentylidene-γ-butyrolactone, (Z)-8a

The crude reaction product, which was prepared starting from ethyl (*Z*)-2-ethenyl-2-heptenoate, (*Z*)-**7e**, was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give pure (*Z*)-**8a** as an oil in 62 % yield. ^{1}H NMR ($CDCl_3$), *δ*: δ 6.23 (1H, tt, *J* = 7.7 and 2.3 Hz, H-1'), 4.31 (2H, t, *J* = 7.4 Hz, H-4), 2.91 (2H, tdt, *J* = 7.4, 2.3 and 2.0 Hz, H-3), 2.72 (2H, t *pseudo*-q, *J* = 7.7 and 2.0 Hz, H-2'), 1.54 - 1.24 (4H, m, H-3' and H-4'), 0.91 ppm (3H, t, *J* = 6.8 Hz, H-5'). MS, *m/z* (%): 154 (30), 125 (100), 99 (10), 97 (15), 86 (10), 81 (25), 79 (40), 77 (12), 67 (22), 55 (18), 53 (36), 43 (27). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.89; H, 9.25.

(Z)-α-benzylidene-γ-butyrolactone, (Z)-8b

GLC analysis of the crude reaction product prepared from ethyl (*Z*)-2-ethenyl-3-phenylpropenoate, (*Z*)-**7g**, showed the presence of two components in a 95.5 : 4.5 molar ratio, which were subsequently identified as (*Z*)- and (*E*)-**8b**, respectively. This crude product was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give pure (*Z*)-**8b** in 62 % yield. M.p. 90 °C. Lit[25] 90 °C. ^{1}H NMR ($CDCl_3$), *δ*: 7.92 - 7.73 (2H, m, H_{orto}), 7.47 - 7.27 (3H, m, H_{meta} and H_{para}), 7.01 (1H, t, *J* = 2.4 Hz, =CH), 4.40 (2H, t, *J* = 7.2 Hz, H-4), 3.14 ppm (2H, dt, *J* = 7.2 and 2.4 Hz, H-3). MS, *m/z* (%): 174 (99), 173 (92), 129 (38), 128 (14), 117 (14), 116 (68), 115 (100), 51 (20), 39 (36).

(E)-α-pentylidene-γ-butyrolactone, (E)-8a

The crude reaction product, which was obtained starting from ethyl (*E*)-2-ethenyl-2-heptenoate, (*E*)-

7e, was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give pure (*E*)-**8a** as an oil in 59 % yield. ^1H NMR ($CDCl_3$), *δ*: 6.75 (1H, tt, *J* = 7.6 and 2.8 Hz, H-1'), 4.38 (2H, t, *J* = 7.5 Hz, H-4), 2.86 (2H, tdt, *J* = 7.5, 2.8 and 1.6 Hz, H-3), 2.20 (2H, t *pseudo*-q, *J* = 7.5 and 1.6 Hz, H-2'), 1.65 - 1.20 (4H, m, H-3' and H-4'), 0.92 ppm (3H, t, *J* = 7.0 Hz, H-5'). MS, *m/z* (%): 154 (8), 125 (24), 112 (8), 99 (100), 97 (9), 86 (36), 81 (30), 67 (18), 55 (13), 54 (15), 53 (23), 41 (39). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.44; H, 9.22.

(E)-α-benzylidene-γ-butyrolactone, (E)-8b

The crude reaction product prepared starting from ethyl (*E*)-2-ethenyl-3-phenylpropenoate, (*E*)-**7g**, was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (98 : 2 *v/v*) as eluant, to give pure (*E*)-**8b** in 65 % yield. M.p. 113.5 -114.5 °C. Lit[25] m.p. 115 - 116 °C. ^1H NMR ($CDCl_3$), *δ*: 7.59 (1H, t, *J* = 2.9 Hz, =CH), 7.56 - 7.35 (5H, m, C_6H_5), 4.48 (2H, t, *J* = 7.3 Hz, H-4), 3.26 ppm (2H, dt, *J* = 7.3 and 2.9 Hz, H-3). MS, *m/z* (%): 174 (100), 173 (89), 130 (12), 129 (40), 128 (15), 117 (12), 116 (65), 115 (97), 51 (16), 39 (20).

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