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Palladium-Mediated Cross-Coupling Reactions Involving 3-Substituted Alkyl (E)-2,3-Dibromopropenoates and Arylzinc or Aryltin Derivatives

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Abstract: Stereodefined unsymmetrically 3,3-disubstituted alkyl 2-bromopropenoates, **5**, were regioselectively prepared by Pd-mediated reactions between 3-alkyl, 3-aryl and 3-alkoxycarbonyl substituted (*E*)-2,3-dibromopropenoates, (*E*)-**7**, and aryl or 1-alkynylzinc chlorides. The stereospecificity of these reactions was found to be dependent on the type of substituent present in the 3-position of (*E*)-**7**. The (*E*)-stereochemistry of compounds **5b**, **5d** and **5i** so prepared was confirmed by their conversion into the corresponding 4-substituted 3-bromocoumarins. Tetrasubstituted α,β-unsaturated esters **10** were then synthesized by Pd-mediated reactions either of (*E*)-**7** with a molar excess of an arylzinc chloride or an aryltributylstannane, or of a compound of general formula **5** with an aryltributylstannane. An examination of the parameters which influence the stereochemistry and the yields of these arylations was made.

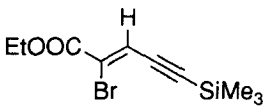
Although transition metal-promoted stereoselective monoarylation, monoalkenylation and monoalkynylation reactions of 1,1-dihaloalkenes[1-5] and trichloroethene[6,7] have been the subject of much study, particular interest has been devoted to the development of stereospecific Pd-mediated monoalkylation and monoalkenylation reactions of (*Z*)- and (*E*)-1,2-dichloroethene[1,8,9] as well as of Pd(0) and Cu(I)-mediated alkynylations of these stereodefined electrophiles.[1,8,9-14] In fact, the cross-coupled products so obtained often represent very useful intermediates for the synthesis of interesting stereodefined bioactive compounds.[1b]

On the contrary, regioselective and stereospecific transition metal-promoted cross-coupling reactions involving stereodefined 1,2-dihaloethene derivatives have not been investigated in detail even though these reactions can be potentially useful from a synthetic point of view. To the best of our knowledge, the first example of this type of reaction involved the synthesis of compound (*Z*)-**1a** by Pd(0) and Cu(I)-mediated reaction of 1-trimethylsilylacetylene, **2**, and ethyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**3a**.[15]

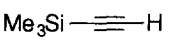
More recently, in the context of our studies on the development of new convenient methods for the preparation of variously substituted α,β-unsaturated esters having very high stereoisomeric purity and their application,[16] we described highly regioselective and stereospecific high yielding syntheses of 3-(1-alkynyl), 3-

aryl and 3-alkyl substituted alkyl (*Z*)- and (*E*)-2-bromopropenoates of general formula (*Z*)- and (*E*)-**4**. These syntheses consisted of Pd-mediated cross-coupling reactions of 1-alkynylzinc chlorides, arylzinc chlorides, aryltributylstannanes or 9-alkyl-9-BBN derivatives with alkyl (*Z*)- and (*E*)-2,3-dibromopropenoates, (*Z*)- and (*E*)-**3**, respectively.[17]

In the course of these studies we discovered that the catalyst precursor obtained by treatment of $Pd(OAc)_2$ with 4 equiv of $AsPPh_3$ in THF at 60 °C for 1 h as well as that consisting of a mixture of 10 % Pd on carbon and 3.9 equiv of $AsPPh_3$ could conveniently replace $Pd(PPh_3)_4$ in the reactions between (*Z*)- and (*E*)-**3** with aryl or 1-alkynylzinc chlorides.[17b] Moreover, we found that 3-aryl substituted alkyl (*Z*)- and (*E*)-2-bromopropenoates, (*Z*)- and (*E*)-**4** (R^1 = aryl), are useful intermediates for the synthesis of trisubstituted α,β-unsaturated esters[17a,c,18] and several types of heterocyclic compounds such as coumarin derivatives,[17c,18] isoaurones,[17c,18] 2,4-disubstituted furans[18] and (*Z*)- and (*E*)-α-arylidene-γ-butyrolactones.[16d,17c]



(*Z*)-**1a**



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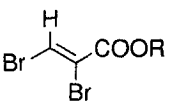
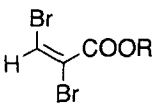
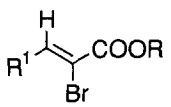


(*Z*)-**3a** : R = Et

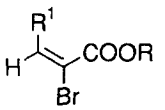
(*Z*)-**3b** : R = Me



(*E*)-**3a** : R = Et

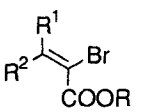


(*Z*)-**4** : R^1 = alkyl, aryl, 1-alkynyl; R = Me, Et



(*E*)-**4** : R^1 = aryl, 1-alkynyl; R = Et

These results prompted us to investigate Pd-mediated cross-coupling reactions involving stereodefined 3-substituted 2,3-dibromopropenoates since these reactions could allow the preparation of stereodefined unsymmetrically 3,3-disubstituted alkyl 2-bromopropenoates, **5**, which, in principle, are synthetically interesting electrophiles not previously described in the literature. In fact, these compounds could represent useful precursors to stereodefined tetrasubstituted α,β-unsaturated esters for which, to the best of our knowledge, only one stereoselective synthesis has been reported so far.[19] Moreover, our investigation could allow the determination of the effect of an alkyl, an aryl or an electron withdrawing group, *e.g.* an alkoxycarbonyl group, in the 3-position of compounds **3** on the regioselectivity, the stereospecificity, the rate and the yield of the cross-coupling reactions involving 2,3-dibromopropenoates.



5

In this paper we wish to report that stereoisomerically pure 3-alkyl, 3-aryl and 3-alkoxycarbonyl substituted alkyl (*E*)-2,3-dibromopropenoates, (*E*)-**7**, which can be easily prepared from the corresponding α,β-acetylenic esters, **6**, undergo highly regioselective Pd-mediated cross-coupling reactions with arylzinc chlorides, **8**, and 1-

alkynylzinc chlorides, **9**, to afford the corresponding stereodefined unsymmetrically 3,3-disubstituted alkyl 2-bromopropenoates, **5**, in modest to satisfactory yields. We will also describe and discuss some side-reactions which occur together with the Pd-mediated arylations of compounds (*E*)-**7** as well as the dependence of the stereospecificity of the monoarylations on the type of dibromide used as electrophile partner. Moreover, we will describe a synthetic application of some compounds of general formula **5**, which also served to demonstrate unambiguously the stereochemistry of these substrates. Finally, the results of some attempts made to convert stereospecifically compounds **5** into tetrasubstituted α,β-unsaturated esters of general formula **10** will be reported and discussed.

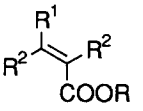
6 : R^1 = alkyl, aryl, COOR; R = Me, Et

(*E*)-**7** : R^1 = alkyl, aryl, COOR; R = Me, Et

R^2–ZnCl

8 : R^2 = aryl

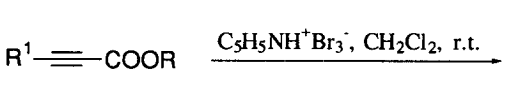
9 : R^2 = 1-alkynyl



10

RESULTS AND DISCUSSION

Compounds (*E*)-**7a-d**, which were used as starting materials for the synthesis of compounds **5**, were prepared in 70 - 98 % yield by reaction of the corresponding α,β-acetylenic esters, **6a-d**, with a slurry of 1.40 equiv of pyridinium bromide perbromide (PBB) in CH_2Cl_2 at 20 °C (eq 1).



6a : $R^1 = C_5H_{11}$; R = Me
6b : $R^1 = CH_3$; R = Et
6c : R^1 = Ph; R = Et
6d : R^1 = COOEt; R = Et

(*E*)-**7a** : $R^1 = C_5H_{11}$; R = Me
(*E*)-**7b** : $R^1 = CH_3$; R = Et
(*E*)-**7c** : R^1 = Ph; R = Et
(*E*)-**7d** : R^1 = COOEt; R = Et

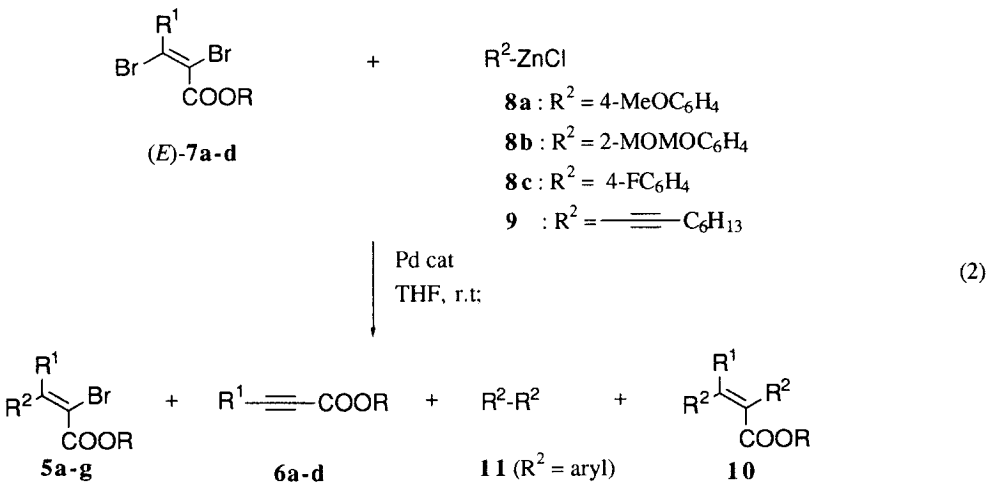
(1)

Crude (*E*)-**7a**, (*E*)-**7b** and (*E*)-**7c**, which were obtained after usual work up, had chemical purity higher than 98 % and were used in the next step without any further purification. On the other hand, crude (*E*)-**7d** was purified by recrystallization. GLC and ^1H NMR analyses showed that (*E*)-**7a-d** had stereoisomeric purity higher than 98 - 99 %. The (*E*)-stereochemistry of **7a** and **7b** was established by comparison between the chemical shift of their H-4 protons with that of the corresponding protons in stereoisomeric mixtures of these dibromides, which were obtained by reaction of CH_2Cl_2 solutions of **6a** and **6b** with 1.05 equiv of Br_2 contaminated by HBr at - 78 °C. The H-4 protons of the (*E*)-stereoisomers resonated at higher fields. On the other hand, the (*E*)-stereochemistry was assigned to **7c** and **7d** taking into account that, in all cases so far examined,[15, 16a,c]

bromination of α,β-acetylenic esters with PBB in CH_2Cl_2 at room temperature affords compounds of (*E*)-configuration.

It interesting to note that compound (*E*)-**7a** could also be obtained in quantitative yield by reaction of **6a** with Br_2 in CH_2Cl_2 at - 78 °C. However, stereoisomeric mixtures of the desired dibromides were obtained when this reaction was carried out at room temperature or at - 78 °C in the presence of small amounts of HBr.

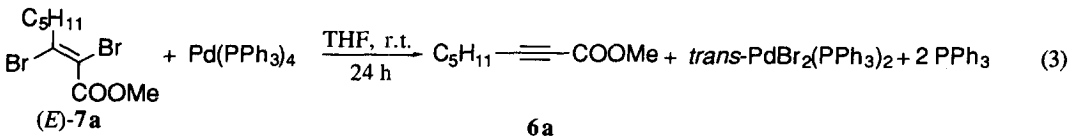
Unsymmetrically 3,3-disubstituted alkyl 2-bromo-3-propenoates of general formula **5** were then prepared by reaction of compounds (*E*)-**7** with 1.1 - 1.6 equiv of an arylzinc chloride, **8**, or an 1-alkynylzinc chloride, **9**, in THF at room temperature, in the presence of 5 mol % of $Pd(PPh_3)_4$ (*Catalyst A*) (eq 2). For the same purpose other catalyst precursors (5 mol %) could be conveniently used, namely that obtained by treatment of $Pd(OAc)_2$ with 4 equiv of $AsPh_3$ in THF at 60 °C (*Catalyst B*)[17b] as well as that consisting of a mixture of 10 % of Pd on carbon in a non-reduced form and 3.9 equiv of $AsPh_3$ (*Catalyst C*).[17b]



(2)

The main results of these coupling reactions are summarized in the Table. Some aspects of these results deserve comment. Firstly, the crude reaction mixtures, which were obtained by reaction of dibromides (*E*)-**7** with compounds **8**, contained the desired cross-coupled products, **5**, together with significant amounts of biaryls, **11**, 8 - 15 % of the α,β-acetylenic esters **6** corresponding to the dibromides used, as well as 2 - 5 % of tetrasubstituted α,β-unsaturated esters, **10**. Compounds of general formula **6** and **10** were also present in the reaction mixtures derived from the reaction between (*E*)-**7** and **9**. Compounds **11** presumably derive from a transmetallation reaction involving compounds **8** and (*E*)-**7** followed by a Pd-promoted homo-coupling reaction. On the other hand, compounds **6** could derive from a *trans*-elimination reaction involving the oxidative-addition complexes which regioselectively result from (*E*)-**7** and the Pd(0) species present in the reaction mixtures. This hypothesis was confirmed by the results of stoichiometric reactions between compounds (*E*)-**7** and $Pd(PPh_3)_4$ in THF. In particular, when (*E*)-**7a** was reacted with 1.0 equiv of $Pd(PPh_3)_4$ in THF at room temperature for 24 h, the reaction mixture was found to be composed of **6a** and (*E*)-**7a** in a *ca.* 92 : 8 molar ratio as well as of *trans*-$PdBr_2(PPh_3)_2$ (eq 3).[20,21] Secondly, all coupling reactions were highly regioselective, but their stereospecificity depended on the type of dibromide used. In fact, when 3-alkyl substituted (*E*)-2,3-dibromopropenoates, *i.e.* (*E*)-**7a** and (*E*)-**7b**, were employed, the desired cross-coupled products, **5**, were stereoisomerically pure (entries 1 -

8, Table).



(3)

On the other hand, crude compounds **5**, which were prepared by Pd-mediated arylations of ethyl (*E*)-2,3-dibromo-3-phenylpropenoate, (*E*)-**7c**, were contaminated by *ca.* 7 % of the corresponding stereoisomers (entries 9 and 11, Table). Moreover, a still higher percentage of undesired stereoisomer (20 %) contaminated the cross-coupled product, (*Z*)-**5j**, which was obtained by reaction of diethyl 2,3-dibromofumarate, (*E*)-**7d**, with 4-methoxyphenylzinc chloride, **8a** (entry 12, Table).

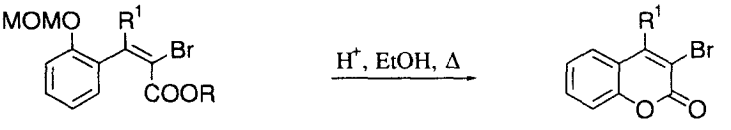
TABLE. Pd-Mediated Cross-Coupling Reactions between Dibromides (*E*)-**7** and Organozinc Halides, **8** or **9a** [a]

Entry	Alkenyl dibromide (*E*)-**7**	Organozinc chloride (equiv)	Catalyst Precursor [b] (mol %)	Reaction time (h)	Product **5**	Yield (%)
1	(*E*)-**7a**	**8a** (1.20)	A (5)	22	(*E*)-**5a**	51
2	(*E*)-**7a**	**8a** (1.10)	B (5)	21.5	(*E*)-**5a**	61
3	(*E*)-**7a**	**8a** (1.10)	C (5)	42	(*E*)-**5a**	43
4	(*E*)-**7a**	**8b** (1.20)	A (7)	71	(*E*)-**5b**	43
5	(*E*)-**7a**	**8c** (1.20)	B (5)	24	(*E*)-**5c**	56
6	(*E*)-**7b**	**8b** (1.20)	B (5)	48	(*E*)-**5d**	24
7	(*E*)-**7a**	**9** (1.20)	B (5)	23	(*E*)-**5e**	57
8	(*E*)-**7b**	**8a** (1.60)	B (5)	24	(*E*)-**5f**	49
9	(*E*)-**7c**	**8c** (1.15)	B (5)	46	(*E*)-**5g** [c]	27
10	(*E*)-**7c**	**8a** (1.35)	A (10)	80	(*E*)-**5h**	18
11	(*E*)-**7c**	**8b** (1.35)	B (5)	72	(*E*)-**5i** [c]	38
12	(*E*)-**7d**	**8a** (1.05)	B (5)	52 [d]	(*Z*)-**5j** [e]	43

(a) Unless otherwise reported these reactions were carried out in THF at room temperature. *(b) Catalyst A* = $Pd(PPh_3)_4$; *Catalyst B* was obtained by treating $Pd(OAc)_2$ with 4 equiv of $AsPh_3$ in THF at 60 °C for 1 h; *Catalyst C* = 10 % Pd/C + 3.9 equiv of $AsPh_3$. *(c)* The crude reaction mixture contained this compound contaminated by *ca.* 7 % of the corresponding (*Z*)-stereoisomer. *(d)* After this period at room temperature the mixture was maintained at 65 °C for 24 h. (e) The crude reaction product contained compounds (*Z*)-**5j** and (*E*)-**5j** in a *ca.* 80 : 20 ratio, respectively.

It must also be noted that the regioselectivity observed for all these couplings was comparable to that previously observed for Pd-mediated cross-coupling reactions involving alkyl (*E*)- and (*Z*)-2,3-dibromopropenoates, (*E*)- and (*Z*)-**3**[17]. Thus, the presence of an alkyl or an aryl group in the β-position of alkyl 2,3-dibromopropenoates does not affect the regiochemistry of the coupling. Thirdly, taking into account that in all cases so far observed the aromatic protons, when in *cis*-position to an alkoxycarbonyl group, resonates at fields

higher than those of the corresponding protons in *trans*-position to the same alkoxycarbonyl group[22], the (*Z*)-stereochemistry was assigned to the main component of the stereoisomeric mixture (80 : 20) of **5j** obtained in entry 12 (Table). On the other hand, the (*E*)-stereochemistry assigned to compounds **5b**, **5d** and **5i**, which were prepared by the above reported general procedure, was confirmed by the fact that, when EtOH solutions of these compounds were refluxed for 3 h in the presence of catalytic amounts of 35 % HCl, 3-bromocoumarins **12a**, **12b** and **12c**, respectively, were obtained in high yield (81 - 98 %) (eq 4). It is worth noting that this simple cyclization reaction allowed the preparation in satisfactory overall yields of variously 4-substituted 3-bromocoumarins starting from α,β-acetylenic esters.



(4)

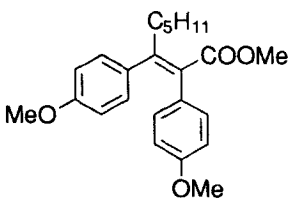
(*E*)-**5b** : $R^1 = C_5H_{11}$; R = Me — **12a** : $R^1 = C_5H_{11}$

(*E*)-**5d** : $R^1 = CH_3$; R = Et — **12b** : $R^1 = CH_3$

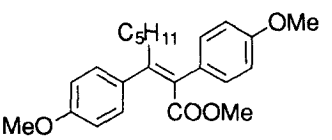
(*E*)-**5i** : R^1 = Ph; R = Et — **12c** : R^1 = Ph

Fourthly, the isolated yields of the reactions mediated by *Catalyst A* were comparable to those of the reactions mediated by *Catalysts B* or *C*. However, they were lower than those of similar reactions involving alkyl (*E*)-2,3-dibromopropenoates, (*E*)-**3**[17b,c]. Such yields were satisfactory for the reactions involving compounds (*E*)-**7a**, (*E*)-**7b** and (*E*)-**7d** (entries 1 - 5, 7, 8 and 12, Table). However, unexpectedly they decreased for the Pd-mediated reactions between (*E*)-**7c** and **8a**, **8b** or **8c** (entries 9 - 11, Table) or between (*E*)-**7b** and **8b** (entry 6, Table). Finally, it is worth noting that the rate of the reactions involving compounds (*E*)-**7a-d** was significantly lower than that of similar reactions involving alkyl (*E*)-2,3-dibromopropenoates, (*E*)-**3**.[17b,c] Thus, it is possible to conclude that the presence of a substituent in the β-position of alkyl (*E*)-2,3-dibromopropenoates does not affect the regiochemistry but gives rise to a decrease either of the rate or the yields of the Pd-mediated cross-coupling reactions.

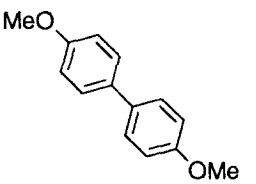
Taking into account these results, attempts were then made to synthesize stereospecifically stereodefined tetrasubstituted α,β-unsaturated esters of general formula **10** by Pd-mediated arylation of compounds (*E*)-**7** or (*E*)-**5** with molar excesses of compounds **8** or an aryltributylstannane. These protocols could allow the preparation of interesting compounds not available by classical olefination procedures. Thus, in a preliminary experiment, compound (*E*)-**7a** was reacted with 2.2 equiv of **8a** and 5 mol % of *Catalyst A* in THF at room temperature for 48 h and at 65 °C for 48 h. GLC/MS analysis of the crude reaction product showed that it was constituted of a mixture of unreacted (*E*)-**7a**, significant amounts of 4,4'-dimethoxybiphenyl, **11a**, methyl (*E*)- and (*Z*)-3-(4-methoxyphenyl)-2-octenoate, (*E*)- and (*Z*)-**13a**, as well as two compounds in a *ca.* 1 : 1 ratio, which were subsequently identified as (*E*)- and (*Z*)-**10a**.



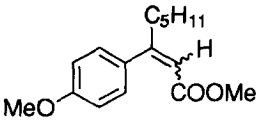
(*E*)-**10a**



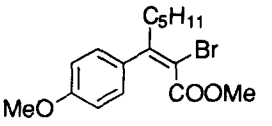
(*Z*)-**10a**



11a

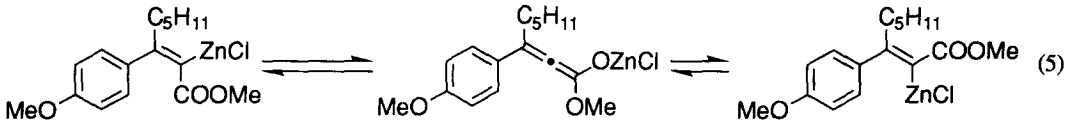


(*Z*)/(*E*)-**13a**



(*E*)-**5a**

Compounds (*Z*)- and (*E*)-**13a** very probably derived from a halogen-metal exchange reaction involving **8a** and (*E*)-**5a**, which was an intermediate reaction product. In fact, according to our previous results[16e], the product, (*E*)-**14a**, so available could be stereochemically unstable (eq 5) and its hydrolysis could give (*Z*)/(*E*)-**13a**.



(5)

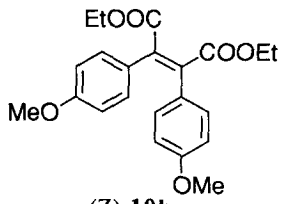
(*E*)-**14a** (*Z*)-**14a**

On the other hand, the fact that the desired compound (*Z*)-**10a** contained the corresponding (*E*)-stereoisomer in a *ca.* 1 : 1 ratio could be interpreted by supposing a conversion of (*E*)/(*Z*)-**14a** into (*E*)/(*Z*)-**5a** followed by a Pd-promoted arylation of the stereoisomeric mixture of this bromo derivative. Compound (*E*)/(*Z*)-**10a** was isolated from the complex mixture obtained in this diarylation reaction in 13 % yield. A higher stereospecificity, but a similar yield, was obtained when (*E*)-**5a** was reacted with 1.5 equiv of **8a** and 5 mol % of *Catalyst B* in a mixture of DMF and THF at room temperature for 24 h. In fact, the crude reaction product contained (*Z*)- and (*E*)-**10a** in a *ca.* 88 : 12 ratio, respectively. Purification of this crude product by MPLC on silica gel allowed us to obtain (*Z*)-**10a** in 13 % yield. Moreover, unexpectedly it was found that stereoisomerically pure (*E*)-**10a** was obtained in 27 % yield by reaction of (*E*)-**7a** with 2.5 equiv of 4-methoxyphenyltributylstannane, **15**, in NMP solution in the presence of 5 mol % of $PdCl_2(PhCN)_2$, 10 mol % of CuI and and 10 mol % of $AsPh_3$[23] at room temperature for 22 h and at 65 °C for 112 h .

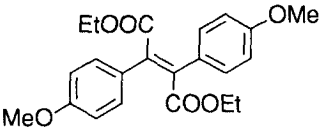
Two subsequent experiments were then carried out to establish if the type of substituent present in the 3-position of alkyl (*E*)-2,3-dibromopropenoates, as well as the type of arylmetal used, could significantly affect the stereospecificity and/or the yield of the Pd-promoted diarylations of compounds (*E*)-**7**. In particular, it was found that, when (*E*)-**7d** was reacted with 3 equiv of **8a** and 5 mol % of *Catalyst B* in THF for 53 h at room temperature, a mixture of (*E*)/(*Z*)-**13b**, diethyl 2,3-di-(4-methoxyphenyl)fumarate, (*E*)-**10b**, and diethyl 2,3-di-(4-methoxyphenyl)maleate, (*Z*)-**10b**, was obtained. Unfortunately, since (*E*)- and (*Z*)-**10b** had very similar retention times on the GLC columns used, we were unable to evaluate their molar ratio. However, purification of the crude reaction product by MPLC on silica gel allowed us to isolate pure (*E*)-**10b** in 39 % yield. On the other hand, a higher yield of a mixture of (*E*)- and (*Z*)-**10b** was obtained by treatment of (*E*)-**7d** with 2.5 equiv of **15**, in NMP in the presence of 5 mol % of $PdCl_2(PhCN)_2$, 10 mol % of CuI and 10 mol % of $AsPh_3$. ^1H NMR analysis of the products, which were obtained after purification by MPLC on silica gel, allowed evaluation that (*E*)- and (*Z*)-**10b** were present in the reaction mixture in a *ca.* 55 : 45 molar ratio, respectively.[24]

In summary, these results showed that: (*i*) when an arylzinc chloride is used as arylating agent, the Pd-promoted diarylation of a 3-alkyl substituted alkyl (*E*)-2,3-dibromopropenoate affords a stereoisomeric mixture of the desired tetrasubstituted α,β-unsaturated ester; (*ii*) the (*E*)/(*Z*) ratio between the stereoisomers of this last

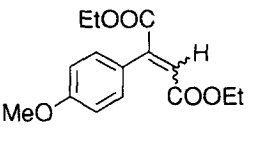
compound is influenced by the experimental conditions and/or the catalyst precursor used; (*iii*) a stereoisomerically pure tetrasubstituted α,β-unsaturated ester having unexpected (*E*)-configuration is obtained by a Pd- and Cu-promoted arylation of the 2-bromo derivative (*E*)-**5a** with an aryltributylstannane; (*iv*) when an aryltributylstannane is used as arylating agent, the yield of the tetrasubstituted α,β-unsaturated ester obtained from a 3-alkyl substituted 2,3-dibromoderivative (*E*)-**7** is higher than that obtained in the reaction involving the corresponding arylzinc chloride; and (*v*) the Pd-promoted diarylations of a 3-alkoxycarbonyl substituted dibromide (*E*)-**7** afford stereoisomeric mixtures of tetrasubstituted α,β-unsaturated esters irrespective of the type of arylating reagent used. However, the yields of these reactions are higher when an aryltributylstannane is employed as arylating agent.



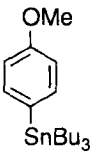
(*Z*)-**10b**



(*E*)-**10b**



(*Z*)/(*E*)-**13b**



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EXPERIMENTAL

All boiling and melting points are uncorrected. Precoated plastic silica gel sheets Merck 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-WAX 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. ^{1}H 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. Methyl 2-octynoate, **6a**, ethyl 3-phenylpropynoate, **6c**, diethyl acetylenedicarboxylate, **6d**, palladium(II) acetate, 10 % palladium on carbon a non-reduced form and $AsPh_3$ were commercially available. Ethyl 2-butynoate, **6b** [b.p. 85 °C/52 Torr; ^{1}H NMR ($CDCl_3$): δ 4.21 (2H, q, J = 7.1 Hz, OCH_2), 1.99 (3H, s, H-4), 1.30 ppm (3H, t, J = 7.1 Hz, O-C-CH_3)] was prepared in 72 % yield by reaction of commercially available 2-butynoic acid with 4 equiv of ethyl iodide in DMF at 20 °C, in the presence of 1.67 equiv of anhydrous K_2CO_3, followed by usual work up. The following compounds were prepared according to the literature: $Pd(PPh_3)_4$[25] and $PdCl_2(PhCN)_2$[26]. 4-Methoxyphenylzinc chloride, **8a**, (2-methoxymethoxy)phenylzinc chloride, **8b**, 4-fluorophenylzinc chloride, **8c**, and 1-octynylzinc chloride, **9**, which were used as 0.3 M slurries in THF, were prepared by reaction of the corresponding aryl and 1-alkynylmagnesium bromides with a slurry of 1.3 equiv of dry $ZnCl_2$ in THF at 0 °C. (2-Methoxymethoxy)phenyl bromide [b. p. 98 - 99 °C/6 Torr; ^{1}H NMR ($CDCl_3$): δ 7.54 (1H, dd, J = 7.9 and 1.5 Hz, H-6'), 7.25 (1H, ddd, J = 8.4, 6.8 and 1.5 Hz, H-4'), 7.14 (1H, dd, J = 8.4 and 1.7 Hz, H-3'), 6.88 (1H, ddd, J = 7.9, 6.8 and 1.7 Hz, H-5'), 5.25 (2H, s, O-CH_2-O), 3.52 ppm (3H, s, O-CH_3)], which was used for

the preparation of the corresponding Grignard reagent, was synthesized from 2-bromophenol according to a general procedure reported in the literature.[27] 4-Methoxyphenyltributylstannane, **15** [b.p. 123 - 125 °C/0.03 Torr; ^{1}H NMR ($CDCl_3$): δ, 7.03 (4H, AA'XX', H_{arom}), 3.80 (3H, s, OMe), 1.70 - 1.40 (8H, m, H-2'), 1.50 - 1.30 (8H, m, H-3'), 1.03 (8H, t, J = 8.2 Hz, H-1'), 0.88 ppm (12H, t, J = 7.1 Hz, H-4'). Anal. Calcd for $C_{19}H_{34}OSn$: C, 57.46; H, 8.63. Found: C, 57.52; H, 8.86] was prepared in 78 % yield by reaction of 4-methoxyphenylmagnesium bromide with 0.80 equiv of Bu_3SnCl in THF under reflux for 19 h, followed by usual work up.

General procedure for the preparation of 3-substituted alkyl (E)-2,3-dibromopropenoates, (E)-7

An α,β-acetylenic ester (20.1 mmol) was added to a suspension of pyridinium bromide perbromide (8.99 g, 28.1 mmol) in dry CH_2Cl_2, which was magnetically stirred under nitrogen at room temperature. The resulting reaction mixture, which was periodically monitored by GLC analysis, was stirred for 6 - 8 days at room temperature. After completion of the reaction, the mixture was poured into a large excess of a 10 % aqueous $Na_2S_2O_3$ solution and extracted with Et_2O. The organic extract was washed with water, a saturated aqueous $NaHCO_3$ solution and water, dried, filtered on Celite and concentrated *in vacuo*. The reaction product so obtained, if not otherwise reported, was used in the next step without any further purification. Methyl (*E*)-2,3-dibromo-2-octenoate, (*E*)-**7a**, ethyl (*E*)-2,3-dibromo-2-butenoate, (*E*)-**7b**, ethyl (*E*)-2,3-dibromo-3-phenylpropenoate, (*E*)-**7c**, and diethyl 2,3-dibromofumarate, (*E*)-**7d** were prepared according to this general procedure.

Methyl (E)-2,3-dibromo-2-octenoate, (E)-7a

This compound, which was prepared in 98 % yield from methyl 2-octynoate, **6a**, according to the above described general procedure, had: ^{1}H NMR ($CDCl_3$): δ 3.85 (3H, s, OMe), 2.72 (2H, t, J = 7.5 Hz, H-4), 1.66 - 1.57 (2H, m, H-5), 1.42 - 1.22 (4H, m, H-6 and H-7), 0.92 ppm (3H, t, J = 6.7 Hz, H-8). MS, *m/z* (%): 316 (2), 314 (2), 312 (1), 235 (18), 177 (16), 121 (32), 93 (100), 59 (22), 41 (43). Anal. Calcd for $C_9H_{14}Br_2O_2$: C, 34.42; H, 4.49. Found: C, 34.40; H, 4.39. GLC and ^{1}H NMR analyses showed that this compound had chemical and stereoisomeric purity higher than 99 %.

It must be noted that this stereoisomerically pure compound was also obtained in quantitative yield by reaction of a solution of **6a** in CH_2Cl_2 at - 78 °C for 6 h with 1 equiv of pure Br_2. On the other hand, when this addition reaction was performed at - 78 °C using Br_2 contaminated by HBr or at room temperature, the product was a stereoisomeric mixture of methyl 2,3-dibromo-2-octenoate. Compound (*Z*)-**7a** had: ^{1}H NMR ($CDCl_3$): δ 5.20 (2H, t, J = 7.5 Hz, H-4), 3.88 ppm (3H, s, OMe).

Ethyl (E)-2,3-dibromo-2-butenoate, (E)-7b

This compound, which was prepared in 98 % yield from ethyl 2-butynoate, **6b**, according to the above described procedure, had: ^{1}H NMR ($CDCl_3$): δ 4.32 (2H, q, J = 7.1 Hz, O-CH_2), 2.50 (3H, s, O-C-CH_3), 1.36 ppm (3H, t, J = 7.1 Hz, H-4). MS, *m/z* (%): 274 (3), 272 (7), 270 (4), 229 (11), 227 (22), 193 (41), 191 (42), 67 (73), 39 (100). Anal. Calcd for $C_6H_8Br_2O_2$: C, 26.50; H, 2.96. Found: C, 26.12; H, 2.68. GLC and ^{1}H NMR analyses showed that this compound had chemical and stereoisomeric purities higher than 99%.

Ethyl (E)-2,3-dibromo-3-phenylpropenoate, (E)-7c

This compound, which was prepared in 94 % yield from ethyl 3-phenylpropynoate, **6c**, according to the above reported general procedure, had: ^{1}H NMR ($CDCl_3$): δ 7.50 - 7.32 (5H, m, Ph), 4.39 (2H, q, J = 7.1 Hz, O-CH_2), 1.40 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 336 (3), 334 (6), 332 (3), 255 (14), 253 (15), 101 (77), 180 (34), 102 (100), 75 (99). Anal. Calcd for $C_{11}H_{10}Br_2O_2$: C, 39.56; H, 3.02. Found: C, 39.28; H, 2.97. GLC and ^{1}H NMR analyses showed that this compound had chemical and stereoisomeric purities higher

than 98 %.

It must be noted that the product, which was obtained by addition of 1 equiv of Br_2 contaminated by a small amount of HBr to a CH_2Cl_2 solution of ethyl 3-phenylpropynoate, **6c**, at - 78 °C, was constituted of a mixture of (*E*)- and (*Z*)-**7c** in a *ca.* 80 : 20 ratio. Compound (*Z*)-**7c** had: ^1H NMR ($CDCl_3$): δ 7.50 - 7.30 (5H, m, Ph), 3.98 (2H, q, J = 7.1 Hz, O-CH_2), 0.91 ppm (3H, t, J = 7.1 Hz, O-C-CH_3).

*Diethyl 2,3-dibromofumarate, (E)-**7d***

The crude reaction compound, which was prepared from diethyl acetylenedicarboxylate, **6d**, according to the above reported general procedure, was recrystallized from hexane to give the title compound in 70 % yield: m.p. 62 - 64 °C. ^1H NMR ($CDCl_3$): δ 4.37 (4H, q, J = 7.1 Hz, O-CH_2), 1.38 ppm (6H, t, J = 7.1 Hz, O-C-CH_3).[Lit. b.p. 145 - 155 °C/11 Torr]. GLC and ^1H NMR analyses showed that this compound was chemically and stereoisomerically pure.

*General procedure for the synthesis of stereodefined 3,3-disubstituted alkyl 2-bromopropenoates, **5**, via palladium-catalyzed cross-coupling reactions between 3-substituted alkyl (E)-2,3-dibromopropenoates, (E)-**7**, and organozinc chlorides*

The preparation of stereodefined 3,3-disubstituted alkyl 2-bromopropenoates was performed using one of the following palladium-catalyst precursors: $Pd(PPh_3)_4$ *(Catalyst A)* (0.58 g, 0.50 mmol); that obtained by heating $Pd(OAc)_2$ (0.11 g, 0.50 mmol) and $AsPh_3$ (0.61 g, 20 mmol) in THF (15 ml) at 60 °C for 1 h *(Catalyst B)*; or that consisting of a mixture of 10 % palladium on carbon in a non-reduced form (0.54 g, 0.50 mmol) and $AsPh_3$ (0.60 g, 1.95 mmol) *(Catalyst C)*. One of these catalyst precursors and a solution of a 3-substituted alkyl (*E*)-2,3-dibromo-2-propenoate, (*E*)-**7** (10.0 mmol) in THF (15 ml) were sequentially added to a slurry of an aryl or a 1-alkynylzinc chloride (11.0 - 16.0 mmol) in THF (60 ml), which was stirred at 0 °C under argon. The molar ratios between compounds (*E*)-**7** and the organozinc chlorides, **8** or **9**, which were used in these reactions are reported in the Table. The resulting mixture was allowed to warm to 20 °C and stirred for the period reported in the Table. The reaction was periodically monitored by GLC analysis of its samples hydrolyzed with a saturated aqueous NH_4Cl solution and extracted with Et_2O. After completion of the reaction, the mixture was treated at 0 °C with an excess of an aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered over Celite, dried and concentrated *in vacuo*. The residue, which was analyzed by GLC/MS, was diluted with the solvent, which was subsequently used for the purification by MPLC on silica gel, and filtered over Celite. The filtrate was concentrated and the residue was purified by MPLC on silica gel.

It must be noted that the crude products, which were obtained in these coupling reactions, contained α,β-acetylenic esters, **6**, which derived from (*E*)-**7**, the desired cross-coupled products, **5**, and small amounts (2 - 5 %) of tetrasubstituted α,β-unsaturated esters, **10**. Moreover, significant amounts of biaryl derivatives, **11**, were also present in the crude products derived from the reactions between compounds (*E*)-**7** and arylzinc chlorides.

Compounds (*E*)-**5a-i** and (*Z*)/(*E*)-**5j** were prepared according to this general procedure.

*Methyl (E)-2-bromo-3-(4-methoxyphenyl)-2-octenoate, (E)-**5a***

The crude product, which was obtained from the reaction between **8a** and (*E*)-**7a** in the presence of *Catalyst A* (entry 1, Table), was purified by MPLC on silica gel, using a mixture of benzene and hexane (70 : 30 *v/v*) as eluant, to give in 51 % yield the title compound as an oil. ^1H NMR ($CDCl_3$): δ 6.97 (4H, AA'XX', H_{arom}), 3.81 (3H, s, OMe), 3.52 (3H, s, OMe), 2.65 (2H, t, J = 7.3 Hz, H-4), 1.45 - 1.25 (6H, m, H-5, H-6 and H-7), 0.85 ppm (3H, t, J = 6.5 Hz, H-8). MS, *m/z* (%): 342 (6), 340 (7), 205 (100), 159 (15), 145 (38), 121 (13), 108 (33), 103 (13), 41 (63). Anal. Calcd for $C_{16}H_{21}BrO_3$: C, 56.32; H, 6.20. Found: C, 56.38; H, 6.30. GLC and ^1H NMR analyses showed that this compound had chemical and stereoisomeric purities higher than 99 %.

It is interesting to note that this same compound was prepared in 61 and 43 % yield by reaction of **8a** with (*E*)-**7a** in the presence of *Catalysts B* and *C*, respectively (entries 2 and 3, Table).

*Methyl (E)-2-bromo-3-[(2-methoxymethoxy)phenyl]-2-octenoate, (E)-**5b***

The crude product, which was obtained from the reaction between **8b** and (*E*)-**7a** in the presence of *Catalyst A* (entry 4, Table), was purified by MPLC on silica gel, using benzene as eluant, to give in 43 % yield the title compound as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.30 - 6.90 (4H, m, H_{arom}), 5.15 (2H, s, O-CH_2-O), 3.47 (3H, s, OMe), 3.45 (3H, s, OMe), 2.68 (2H, t, J = 7.3 Hz, H-4), 1.50 - 1.10 (6H, brm, H-5, H-6 and H-7), 0.85 ppm (3H, t, J = 6.8 Hz, H-8). MS, *m/z* (%): 372 (0.4), 370 (0.4), 215 (7), 159 (7), 131 (11), 115 (8), 90 (3), 77 (3), 45 (100). Anal. Calcd for $C_{17}H_{23}BrO_4$: C, 54.97; H, 6.24. Found: C, 55.27; H, 6.30. GLC analysis showed that this compound had chemical and stereoisomeric purities higher than 99 %.

*Methyl (E)-2-bromo-3-(4-fluorophenyl)-2-octenoate, (E)-**5c***

The crude product, which was obtained from the reaction between **8c** and (*E*)-**7a** in the presence of *Catalyst B* (entry 5, Table), was purified by MPLC on silica gel, using a mixture of hexane and benzene (85 : 15 *v/v*) as eluant, to give in 56 % yield the title compound as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.20 - 6.95 (4H, m, H_{arom}), 3.51 (3H, s, OMe), 2.65 (2H, t, J = 7.3 Hz, H-4), 1.50 - 1.10 (6H, brm, H-5, H-6 and H-7), 0.85 ppm (3H, t, J = 6.4 Hz, H-8). MS, *m/z* (%): 330 (3), 328 (3), 217 (6), 193 (67), 179 (11), 147 (42), 133 (100), 109 (40), 59 (32). Anal. Calcd for $C_{15}H_{18}BrFO_2$: C, 54.72; H, 5.51. Found: C, 55.08; H, 5.51. GLC and ^{1}H NMR analyses showed that this compound was chemically and stereoisomerically pure.

*Ethyl (E)-2-bromo-3-[(2-methoxymethoxy)phenyl]-2-butenoate, (E)-**5d***

The crude product, which was obtained from the reaction between **8b** and (*E*)-**7b** in the presence of *Catalyst B* (entry 6, Table), was purified by MPLC on silica gel, using a mixture of hexane and ethyl acetate (93 : 7 *v/v*) as eluant, to give in 24 % yield the title compound as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.34 - 6.88 (4H, m, H_{arom}), 5.16 (2H, s, O-CH_2-O), 3.90 (2H, q, J = 7.1 Hz, COO-CH_2), 3.45 (3H, s, OMe), 2.28 (3H, s, H-4), 0.86 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 330 (1), 328 (1), 269 (3), 267 (3), 204 (32), 176 (11), 159 (15), 131 (16), 45 (100). Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.20. Found: C, 51.03: H, 4.96. GLC analysis showed that this compound was chemically and stereoisomerically pure.

*Methyl (E)-2-bromo-4-pentyl-2-undecen-4-ynoate, (E)-**5e***

The crude product, which was obtained from the reaction between **9** and (*E*)-**7a** in the presence of *Catalyst B* (entry 7, Table), was purified by MPLC on silica gel, using a mixture of hexane and benzene (85 : 15 *v/v*) as eluant, to give in 57 % yield the title compound as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 3.82 (3H, s, OMe), 2.47 (2H, *pseudo* t, J = 7.7 Hz, H-1'), 2.39 (2H, t, 6.9 Hz, H-6), 1.70 - 1.45 (4H, m, H-2' and H-7), 1.45 - 1.20 (10H, brm, H-8, H-9, H-10, H-3' and H-4'), 1.00 - 0.82 ppm (6H, m, H-11 and H-5'). MS, *m/z* (%): 344 (1), 342 (1), 299 (4), 259 (29), 257 (29), 119 (17), 105 (31), 91 (41), 41 (100). Anal. Calcd for $C_{17}H_{27}BrO_2$: C, 59.48; H, 7.93. Found: C, 58.94, H, 7.78. GLC and ^{1}H NMR analyses showed that this compund was chemically and stereoisomerically pure.

*Ethyl (E)-2-bromo-3-(4-methoxyphenyl)-2-butenoate, (E)-**5f***

The crude product, which was obtained from the reaction between **8a** and (*E*)-**7b** in the presence of *Catalyst B* (entry 8, Table), was purified by MPLC on silica gel, using a mixture of hexane and benzene (60 : 40 *v/v*) as eluant, to give in 49 % yield the title compound as pale yellow crystalline solid: m.p. 40 - 41 °C. ^{1}H NMR ($CDCl_3$): δ 6.99 (4H, AA'XX', H_{arom}), 4.00 (2H, q, J = 7.1 Hz, O-CH_2), 3.80 (3H, s, OMe), 2.29 (3H, s, H-4), 0.99 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 300 (20), 298 (21), 255 (15), 254 (35), 252 (36),

173 (39), 145 (71), 131 (45), 108 (100). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 52.43; H, 5.00. GLC and ^1H NMR analyses showed that this compound had chemical and stereoisomeric purities higher than 99 %.

*Ethyl (E)-2-bromo-3-(4-fluorophenyl)-3-phenylpropenoate, (E)-**5g***

GLC/MS analysis of the crude product, which was obtained from the reaction between **8c** and (*E*)-**7c** in the presence of *Catalyst B* (entry 9, Table), showed that it contained (*E*)-**5g** contaminated by *ca.* 20 % of 4,4'-difluorobiphenyl, **11c**, and *ca.* 7 % of (*Z*)-**5g**. This crude product was purified by MPLC on silica gel, using a mixture of hexane and benzene (70 : 30 *v/v*) as eluant, to give in 27 % yield the title compound as a crystalline solid: m.p. 83 - 84 °C (from hexane). ^1H NMR ($CDCl_3$): δ 7.42 - 7.22 (5H, m, Ph), 7.22 - 6.90 (4H, m, H-2', H-3', H-5' and H-6'), 4.08 (2H, q, J = 7.1 Hz, O-CH_2), 1.04 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 350 (10), 348 (11), 225 (10), 196 (100), 194 (23), 183 (16), 123 (26), 105 (35), 75 (22). Anal. Calcd for $C_{17}H_{14}BrFO_2$: C, 58.47; H, 4.04. Found: C, 58.11; H, 3.95. GLC analysis showed that this compound was chemically and stereoisomerically pure.

*Ethyl (E)-2-bromo-3-(4-methoxyphenyl)-3-phenylpropenoate, (E)-**5h***

The crude product, which was obtained from the reaction between **8a** and (*E*)-**7c** in the presence of *Catalyst A* (entry 10, Table), was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (90 : 10 v/v) as eluant, to give in 18 % yield the title compound as a colourless crystalline solid: m.p. 70 - 71 °C. ^1H NMR ($CDCl_3$): δ 7.45 - 7.25 (5H, m, Ph), 6.95 (4H, AA'XX', H-2', H-3', H-5' and H-6'), 4.08 (2H, q, J = 7.1 Hz, O-CH_2-C), 3.78 (3H, s, OMe), 1.04 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 362 (38), 360 (40), 253 (15), 237 (32), 208 (56), 193 (47), 166 (21), 165 (100), 105 (21). Anal. Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74. Found: C, 59.79; H, 4.67. GLC analysis showed that this compound was chemically pure.

*Ethyl (E)-2-bromo 3-[(2-methoxymethoxy)phenyl]-3-phenylpropenoate, (E)-**5i***

GLC/MS analysis of the crude product, which was obtained from the reaction between **8b** and (*E*)-**7c** in the presence of *Catalyst B* (entry 11, Table), showed that it contained (*E*)-**5i** contaminated by *ca.* 7 % of the corresponding (*Z*)-stereoisomer and by a significant amount of 2,2'-di(2-methoxymethoxy)biphenyl, **11b**. This crude product was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (90 : 10 *v/v*) as eluant to give in 38 % yield the title compound contaminated by *ca* 25 % of **11b**. Compound (*E*)-**5i** had: MS, *m/z* (%): 392 (0.2), 390 (0.2), 279 (3), 267 (7), 266 (36), 221 (17), 194 (20), 165 (35),45 (100). This product was used in the next step without any further purification.

*Diethyl 2-bromo-3-(4-methoxyphenyl)fumarate, (Z)-**5j**, and diethyl 2-bromo-3-(4-methoxyphenyl)maleate, (E)-**5j***

GLC/MS analysis of the crude product, which was obtained from the reaction between **8a** and (*E*)-**7d** in the presence of *Catalyst B* (entry 12, Table), showed that it contained two compounds, subsequently identified as (*Z*)-**5j** and (*E*)-**5j** in a *ca.* 80 : 20 molar ratio, respectively. This crude product was purified by MPLC on silica gel, using a mixture of hexane and ethyl acetate (90 : 10 v/v) as eluant to give in 43 % yield a stereoisomeric mixture of (*Z*)- and (*E*)-**5j** in a 80 : 20 ratio, respectively. Anal. Calcd for $C_{15}H_{14}BrO_5$: C, 50.87 ; H, 3.98 . Found: C, 51.07; H, 3.89. Compound (*Z*)-**5j** had: ^1H NMR ($CDCl_3$): δ 7.07 (4H, AA'XX', H_{arom}), 4.32 (2H, q, J = 7.1 Hz, O-CH_2), 4.09 (2H, q, J = 7.1 Hz, O-CH_2), 3.81 (3H, s, OMe), 1.33 (3H, t, J = 7.12 Hz, O-C-CH_3), 1.05 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). Compound (*E*)-**5j** had: ^1H NMR ($CDCl_3$): δ 7.17 (4H, AA'XX', H_{arom}), 4.33 (2H, q, J = 6.9 Hz, O-CH_2), 4.26 (2H, q, J = 7.0 Hz, O-CH_2), 3.83 (3H, s, OMe), 1.37 (3H, t, J = 6.9 Hz, O-C-CH_3), 1.28 ppm (3H, t, J = 7.0 Hz, O-C-CH_3).

*Stoichiometric reaction between methyl (E)-2,3-dibromo-2-octenoate, (E)-**7a** and $Pd(PPh_3)_4$*

A solution of compound (*E*)-**7a** (0.63 g, 2.0 mmol) and $Pd(PPh_3)_4$ (2.31 g, 2.0 mmol) in dry THF (35 ml)

was stirred under argon at room temperature. After 1 h the mixture became heterogeneous. After 24 h a GLC/MS analysis of a sample of the supernatant liquid showed the presence of methyl 2-octynoate, **6a**, and (*E*)-**7a** in a *ca.* 92 : 8 molar ratio, respectively. The reaction mixture was then filtered and the yellow solid so obtained was washed with hexane dried *in vacuo*. The crystalline solid so obtained (0.68 g) was identified as *trans*-dibromobis(triphenylphosphine)palladium(II). Anal. Calcd for $C_{36}H_{30}Br_2Pd$: C, 54.68; H, 3.82. Found: C, 55.03; H, 4.09. IR (KBr): 1480, 1440, 1175, 1165, 1160, 1095, 1090, 1060, 1000, 995, 845, 740, 700, 690, 615, 520, 505, 490, 455, 430 cm^{-1}. The IR spectrum was in good agreement with that of an authentic sample of *trans*-dibromobis(triphenylphosphine)palladium(II) prepared according to the method used for the preparation of *trans*-dichlorobis(triphenylphosphine)palladium(II)[28].

General procedure for the preparation of 3-bromo-4-arylcoumarins, ***12***

A solution of a 3-substituted alkyl (*E*)-2-bromo-3-[(2-methoxymethoxy)phenyl]propenoate, (*E*)-**5b**, (*E*)-**5d**, or (*E*)-**5i** (5.39 mmol), in EtOH (30 ml) containing three drops of 35 % HCl was refluxed for 3 h. It was then cooled to room temperature, diluted with water (5 ml) and concentrated *in vacuo*. Water (20 ml) was added to the residue and the mixture was repeatedly extracted with Et_2O. The collected organic extracts were washed with water to neutrality, dried and concentrated *in vacuo*. The solid residue was purified by recrystallization to give the pure title compounds.

3-Bromo-4-pentylcoumarin, ***12a***

This compound, recrystallyzed from hexane, was prepared in 81 % yield from (*E*)-**5b** according to the above reported general procedure: m. p. 54 -55 °C. ^1H NMR ($CDCl_3$): δ 7.80 - 7.15 (4H, m, H_{arom}), 3.03 (2H, t, J = 7.3 Hz, H-1'), 1.80 - 1.15 (6H, brm, H-2', H-3' and H-4'), 0.94 ppm (3H, t, J = 6.8 Hz, H-5'). MS, *m/z* (%): 296 (11), 294 (12), 240 (58), 238 (62), 215 (16), 159 (53), 131 (65), 102 (100), 77 (44). Anal. Calcd for $C_{14}H_{15}BrO_2$: C, 56.97; H, 5.12. Found: 57.36; H, 5.27.

3-Bromo-4-methylcoumarin, ***12b***

This compound, recrystallized from 95 % EtOH, was prepared in 96 % yield from (*E*)-**5d** according to the above reported general procedure: m. p. 114 °C. ^1H NMR ($CDCl_3$): δ 7.75 - 7.26 (4H, m, H_{arom}), 2.64 ppm (3H, s, CH_3). MS, *m/z* (%): 240 (42), 238 (44), 212 (16), 210 (18), 159 (33), 131 (100), 103 (57), 77 (46), 51 (39). Anal. Calcd for $C_{10}H_7BrO_2$: C, 50.24; H, 2.95. Found: C, 50.67; H, 2.89.

3-Bromo-4-phenylcoumarin, ***12c***

This compound, recrystallized from CH_3OH, was prepared in 98 % yield from crude (*E*)-**5i** according to the above reported general procedure: m.p. 153 - 154 °C. ^1H NMR ($CDCl_3$): δ 7.80 - 7.47 (5H, m, Ph), 7.47 - 7.00 ppm (4H, m, H_{arom}). MS, *m/z* (%): 302 (26), 300 (24), 274 (14), 272 (15), 221 (23), 165 (100), 163 (33), 139 (18), 39 (26). Anal. Calcd for $C_{15}H_9BrO_2$: C, 59.83; H, 3.01. Found: C, 59.95; H, 2.95.

Methyl (Z)- and (E)-2,3-di-(4-methoxyphenyl)-2-octenoate, ***10a***

Procedure A. Methyl (*E*)-2,3-dibromo-2-octenoate, (*E*)-**7a** (4.70 g, 15.0 mmol) in THF (20 ml) was added to a mixture of **8a** (33.0 mmol) and $Pd(PPh_3)_4$ (0.87 g, 0.75 mmol) in THF (70 ml) cooled to 0 °C and the resulting mixture was stirred under nitrogen for 48 h at room temperature and for 48 h at 65 °C. It was then cooled to room temperature and worked up according to the procedure followed for the preparation of compounds (*E*)-**5**. GLC/MS analysis of the crude reaction product showed that it was constituted of a mixture of unreacted (*E*)-**7a**, 4,4'-dimethoxybiphenyl, **11a**, two compounds, which, on the basis of their MS spectra, corresponded to methyl (*Z*)- and (*E*)-3-(4-methoxyphenyl)-2-octenoate, (*Z*)- and (*E*)-**13a**, and two compounds, which were subsequently identified as methyl (*E*)- and (*Z*)-2,3-di-(4-methoxyphenyl)-2-octenoate, (*E*)- and (*Z*)-**10a**, in a *ca.* 1 : 1 ratio, respectively. Purification of this crude reaction product by MPLC on silica gel, using a mixture of

benzene and hexane (90 : 10 *v/v*) as eluant, followed by a second purification by MPLC, using benzene as eluant, and concentration of the intermediate chromatographic fractions allowed to obtain (*E*)-**10a** (0.16 g): ^{1}H NMR ($CDCl_3$): δ 7.00 - 6.86 (4H, m, H_{arom}), 6.74 - 6.60 (4H, m, H_{arom}), 3.77 (3H, s, OMe), 3.74 (3H, s, OMe), 3.72 (3H, s, OMe), 2.59 (2H, t, J = 7.9 Hz, H-4), 1.50 - 1.08 (6H, m, H-5, H-6 and H-7), 0.84 ppm (3H, t, J = 6.5 Hz, H-8). MS, *m/z* (%): 369 (13), 368 (59), 337 (6), 293 (100), 279 (37), 251 (76), 165 (48), 159 (75), 121 (89). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.67. Found: C, 74.65; H, 8.02. On the other hand, concentration of the last eluted chromatographic fractions of the second MPLC allowed to obtain (*Z*)-**10a** (0.68 g), which was contaminated by *ca.* 10 % of (*E*)/(*Z*)-**13a**. Compound (*Z*)-**10a** had: ^{1}H NMR ($CDCl_3$): δ 7.30 - 7.17 (4H, m, H_{arom}), 6.97 - 6.83 (4H, m, H_{arom}), 3.83 (3H, s, OMe), 3.82 (3H, s, OMe), 3.43 (3H, s, OMe), 2.34 (2H, t, J = 7.3 Hz, H-4), 1.35 - 1.05 (6H, m, H-5, H-6 and H-7), 0.77 ppm (3H, t, J = 6.4 Hz, H-8). MS, *m/z* (%): 369 (13), 368 (58), 294 (22), 293 (95), 279 (36), 251 (71), 165 (44), 159 (78), 121 (100). Thus, compounds (*E*)- and (*Z*)-**10a** were obtained in a *ca.* 13 % overall yield. On a SE-30 GLC column compound (*Z*)-**10a** had retention time higher than that of corresponding (*E*)-stereoisomer.

Procedure B. A solution of compound (*E*)-**5a** (4.37 g, 12.8 mmol) in THF (20 ml) was added to a mixture of **8a** (19.2 mmol) in THF (50 ml) and the catalyst precursor prepared from $Pd(OAc)_2$ (0.14 g, 0.64 mmol) and $AsPh_3$ (0.78 g, 2.56 mmol) in THF (15 ml) at 60 °C. DMF (60 ml) was added to this mixture maintained under stirring at 0 °C. The resulting mixture was stirred at room temperature for 24 h and then quenched. The crude reaction products, which were obtained after usual work up,were diluted with a mixture of hexane and Et_2O (70 : 30 v/v) and filtered over Celite. GLC analysis of the filtrate showed the presence of (*Z*)- and (*E*)-**10a** in a *ca.* 88 : 12 ratio, respectively. The filtrate was then concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (70 : 30 *v/v*) as eluant. Concentration of the first eluted chromatographic fractions allowed to obtain pure compound (*Z*)-**10a** (0.61 g, 13 % yield). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.67. Found: C, 74.83; H, 7.38. The spectral properties of this compound were in good agreement with those reported above.

On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate (*E*)/(*Z*)-7,8-dimethoxycarbonyl-6,9-di-(4-methoxyphenyl)-6,8-tetradecadiene. ^{1}H NMR ($CDCl_3$): δ 7.35 - 6.70 (8H, m, H_{arom}), 3.79 (3H, s, OMe), 3.77 (3H, s, OMe), 3.76 (3H, s, OMe), 3.53 (3H, s, OMe), 2.85 (2H, t, J = 7.3 Hz, =C-CH_2), 2.20 (2H, t, J = 7.5 Hz, =C-CH_2), 1.55 -1.00 (12H, brm, H-2, H-3, H-4, H-11,H-12 and H-13), 0.88 (3H, t, J = 6.2 Hz, H-1 or H-14), 0.79 ppm (3H, t, J = 6.3 Hz, H-14 or H-1). Ms, *m/z* (%): 341 (0.3), 191 (1), 149 (4), 136 (6), 121 (8), 95 (15), 93 (11), 81 (51), 69 (100).

Procedure C. A dried flask flushed with argon was charged with $PdCl_2(PhCN)_2$ (0.23 g, 0.59 mmol), CuI (0.23 g, 1.19 mmol), $AsPh_3$ (0.36 g, 1.19 mmol), (*E*)-**7a** (3.74 g, 11.9 mmol) and degassed N-methylpyrrolidinone (NMP) (25 ml) dried over molecular sieves. A degassed solution of 4-methoxyphenyltributylstannane, **15** (11.82 g, 29.7 mmol) in dry NMP (10 ml) was then added and the mixture, which was periodically monitored by GLC, was stirred for 22 h at room temperature and for 112 h at 65 °C. It was then cooled to 20 °C, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The collected organic extracts were washed with water, filtered over Celite and concentrated *in vacuo*. The residue was diluted with Et_2O (100 ml) and stirred at room temperature for 6 h with a large excess of a semisaturated aqueous KF solution. The mixture was filtered over Celite and the filtrate was repeatedly extracted with Et_2O. The collected organic extracts were dried and concentrated *in vacuo*. The residue was diluted with a mixture of hexane and Et_2O (70 : 30 *v/v*) as eluant and filtered over Celite. GLC/MS analysis of the filtrate showed the presence of unreacted (*E*)-**7a**, **11a**, which was the main component, and (*E*)-**10a**. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (85 : 15 *v/v*) as eluant to give (*E*)-**10a** (1.20 g, 27 % yield). The spectral properties of this compound

were in very good agreement with those of (*E*)-**10a** obtained by *Procedure A*.

*Diethyl 2,3-di-(4-methoxyphenyl)fumarate, **10b***

Procedure A. A solution of diethyl 2,3-dibromofumarate, (*E*)-**7d** (3.30 g, 10.0 mmol) in THF (30 ml) was added to a mixture of **8a** (30 mmol) in THF (100 ml) and the catalyst precursor prepared from $Pd(OAc)_2$ (0.11 g, 0.5 mmol) and $AsPh_3$ (0.69 g, 2.25 mmol) in THF (15 ml) at 60 °C, which was stirred at 0 °C under argon. The resulting mixture, which was periodically monitored by GLC analysis, was stirred at room temperature for 53 h and then quenched. The crude reaction product, which was obtained after usual work up, was diluted with a mixture of hexane and ethyl acetate (80 : 20 *v/v*) and filtered over Celite. GLC/MS analysis of the filtrate showed the presence of 4,4'-dimethoxybiphenyl, **11a**, diethyl (*E*)/(*Z*)-2-(4-methoxyphenyl)fumarate, (*E*)/(*Z*)-**13b**, diethyl 2,3-di-(4-methoxyphenyl)maleate, (*Z*)-**10b**, and diethyl 2,3-di-(4-methoxyphenyl)fumarate, (*E*)-**10b**. Since these two last stereoisomers had very similar retention times on the GLC columns used, it was very difficult to establish their molar ratio. (*E*)/(*Z*)-**13b** had MS, *m/z* (%): 279 (16), 278 (96), 233 (16), 206 (88), 205 (54), 177 (100), 161 (26), 117 (24), 109 (27). The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and ethyl acetate (80 : 20 *v/v*) as eluant to give the title compound as a colourless crystalline solid (1.48 g, 39 % yield): m.p. 94 -96 °C (from CH_3OH). ^1H NMR ($CDCl_3$): δ 7.11 (8H, AA'XX', H_{arom}), 4.04 (4H, q, J = 7.1 Hz, O-CH_2), 3.81 (6H, s, OMe), 1.01 ppm (6H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 385 (17), 384 (71), 255 (16), 239 (24), 238 (26), 223 (49), 195 (22), 165 (24), 135 (100). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.77; H, 6.28. ^1H NMR analysis showed that this compound was stereoisomerically pure.

Procedure B. The crude reaction mixture, which was obtained by reaction of a mixture of $PdCl_2(PhCN)_2$ (0.19 g, 0.5 mmol), CuI (0.19 g, 1.0 mmol), $AsPh_3$ (0.31 g, 1.0 mmol), (*E*)-**7d** (3.30 g, 10.0 mmol) in dry NMP (20 ml) with a degassed solution of **15** (9.93 g, 25.0 mmol) in dry NMP (20 ml) at room temperature for 46 h and at 45 °C for 46 h, was cooled to 20 °C and worked up according to *Procedure C* followed in the preparation (*Z*)-**10a**. The crude product was purified by MPLC on silica gel, using a mixture of hexane and ethyl acetate (80 : 20 *v/v*) as eluant. Concentration of the first eluted chromatographic fractions afforded stereoisomerically pure (*E*)-**10b** (0.93 g). The physical and spectroscopic properties of this compound were in very good agreement with those of (*E*)-**10b** prepared according to *Procedure A*. On the other hand, concentration of the intermediate chromatographic fractions afforded a mixture of (*Z*)- and (*E*)-**10b** (1.39 g): m.p. 62 - 70 °C. ^1H NMR analysis showed that (*Z*)- and (*E*)-**10b** were in a *ca.* 91 : 9 ratio, respectively. Compound (*Z*)-**10b** had ^1H NMR ($CDCl_3$): δ 6.87 (8H, AA'XX', H_{arom}), 4.29 (4H, q, J = 7.1 Hz, O-CH_2), 3.75 (6H, s, OMe), 1.30 ppm (6H, t, J = 7.1 Hz, O-C-CH_3). On the basis of these data it was possible to evaluate that compounds (*E*)- and (*Z*)-**10b**, which were obtained in 60 % overall yield, were present in the reaction product in a *ca.* 55 : 45 molar ratio, respectively.

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