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SELECTIVE PREPARATION OF NON-SYMMETRICALLY SUBSTITUTED DIVINYLBENZENES BY PALLADIUM-CATALYSED ARYLATIONS OF ALKENES WITH BROMOBENZOIC ACID DERIVATIVES

ALWYN SPENCER

Central Research Laboratories, Ciba-Geigy AG, CH-4002 Basel (Switzerland)

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Summary

Palladium-catalysed arylation of alkenes with the three bromobenzoic acids or their acyl chlorides provides an efficient and selective method for the preparation of non-symmetrically substituted divinylbenzene derivatives. In the presence of palladium acetate and a phosphorus ligand the free acids react as aryl bromides, with the exception of 2-bromobenzoic acid. If palladium acetate is used alone as catalyst, all three bromobenzoyl chlorides react only as aroyl chlorides. Using two different alkenes a given non-symmetrically substituted divinylbenzene can be prepared by four different routes, allowing for an optimum choice of synthesis path. Substituent effects in the aromatic derivatives and the reactivity of the alkenes in arylation are the principal features to be taken into account. The reaction pathway can generally be chosen to give excellent yields in short reaction times at low palladium concentrations.

Introduction

We recently described methods for the palladium-catalysed arylation of activated alkenes with aroyl chlorides [1] and aryl bromides [2] which can be carried out at very low catalyst concentrations. Heck has reported the preparation of non-symmetrically substituted divinyl-benzene derivatives by arylation of alkenes with bromoiodobenzenes [3]. We report here the use of the three bromobenzoic acids or their acyl chlorides for the same purpose. This method is more versatile than that of Heck, can be carried out in very good yields at significantly lower catalyst concentration, and has the added advantage that the bromobenzoic acids are cheaper and more readily available than the bromoiodobenzenes.

Results and discussion

The general method is illustrated in Scheme 1, which shows two of the four possible routes to a given 1,4-divinyl-benzene derivative, starting from 4-bromoben-

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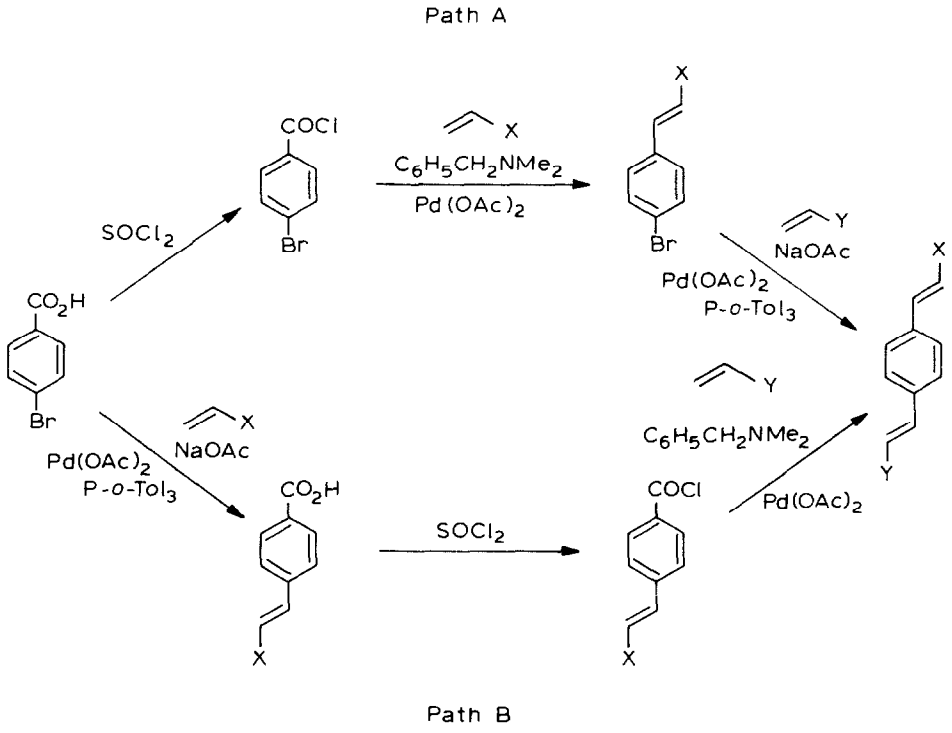
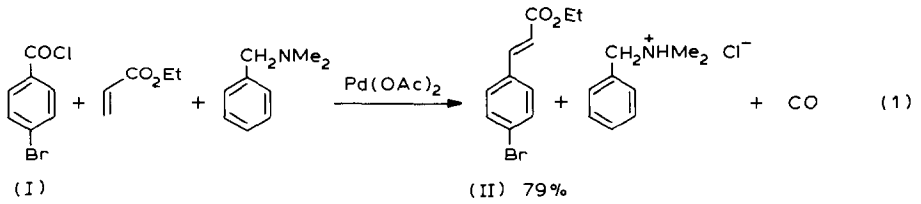


SCHEME 1. General method for selective diarylation using 4-bromobenzoic acid (X, Y = activating groups).

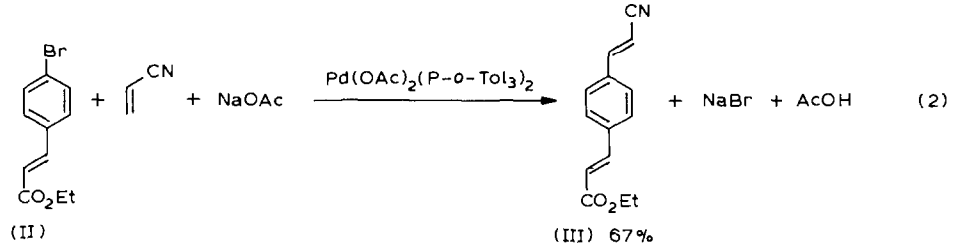
zoic acid. The other two routes are obtained by reversing the order in the Scheme in which the two alkenes are introduced. Each route involves three separate reactions, comprising two arylations and the conversion at the appropriate point of a carboxylic acid to the acid chloride. The bases given in the Scheme are used in stoichiometric quantity or in a slight excess over this. The choice of the appropriate base for each arylation is important (see below and references 1 and 2).

The versatility of the method is largely dependent on the fact that the three possible bromobenzoyl chlorides in the presence of palladium acetate alone as catalyst react only via the acid chloride group. On the other hand, 3- and 4-bromobenzoic acids can be made to react in the first arylation in the Scheme via the C–Br bond only, since the free carboxylic acid group does not enter into these arylation reactions. A triarylphosphine ligand is needed here. 2-Bromobenzoic acid does not react catalytically owing to interaction of the carboxylate group with the palladium (see below). In this case, only path A of the Scheme can be used, reducing the number of possible routes to the end-product to two.

All arylations were carried out at a palladium concentration of 0.1 mol% relative to the aromatic compound, though lower concentrations can be used [1,2]. 4-Bromobenzoic acid was converted to 4-bromobenzoyl chloride (I) with thionyl chloride in 95% yield. Arylation of ethyl acrylate with I catalysed by palladium acetate gave (*E*)-ethyl 4-bromocinnamic acid (II) in a yield of 79% (eq. 1).

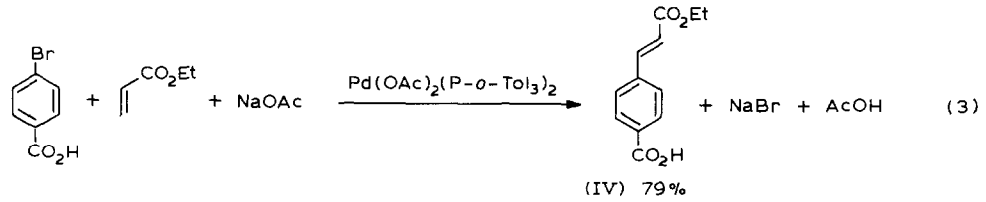


Compound II reacts with acrylonitrile in the presence of palladium acetate and tri(*o*-tolyl)phosphine as ligand to give (*E*,*E*)-1-(2-ethoxycarbonylvinyl)-4-(2-cyanovinyl)benzene (III) in 67% yield (eq. 2).

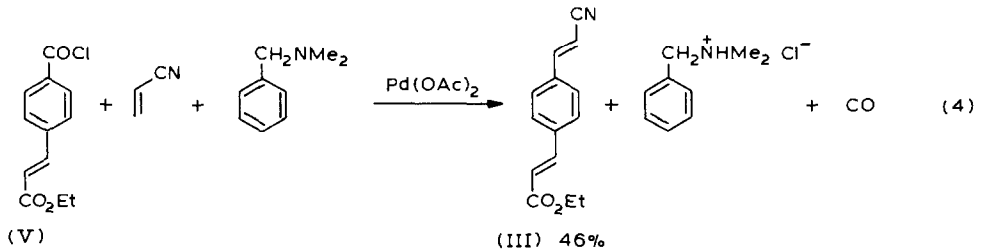


This gives a total yield of 50% over three stages. For comparison the same compound was prepared by two of the other three possible routes.

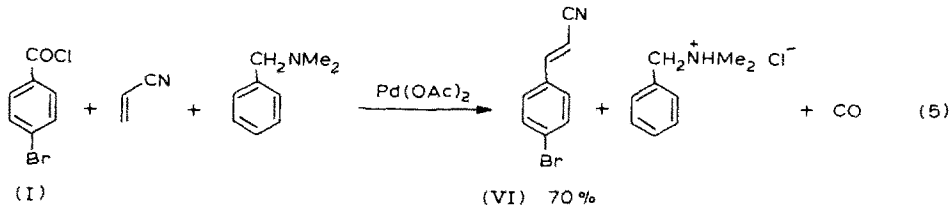
4-Bromobenzoic acid reacted with ethyl acetate to give (*E*)-ethyl 4-hydroxycarbonylcinnamate (IV) in 79% yield (eq. 3).



IV gave on reaction with thionyl chloride (*E*)-ethyl 4-chlorocarbonylcinnamate (V) in 88% yield. This reacted with acrylonitrile to give III as the (*E*,*E*)-isomer in 46% yield (eq. 4).

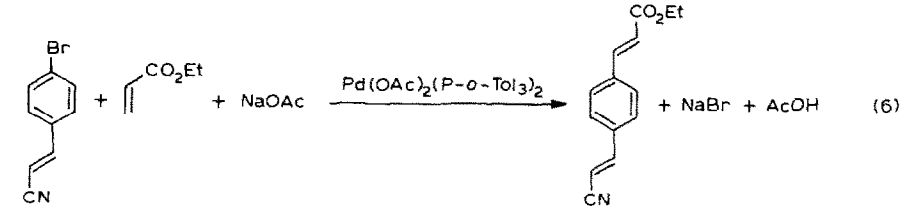


The overall yield for the three stages is thus only 32% by this route. In the third route tried, the order in which the alkenes were used was reversed. Compound I reacted with acrylonitril to give 4-bromocinnamonitrile (VI) in 70% yield (eq. 5).



(I) (VI) 70%

Reaction of VI with ethyl acrylate gave III as the (*E*,*E*)-isomer in a yield of 73% (eq. 6). The overall yield here is 49% over three stages.

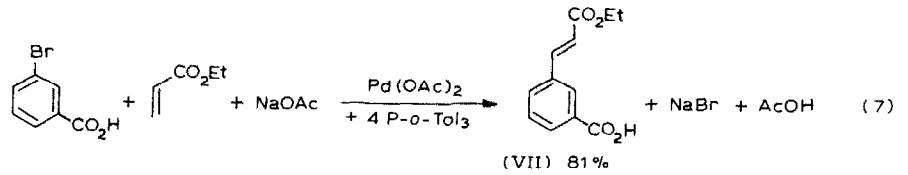


(VI) (III) 73%

In this case the crude product contained 14% of the isomer having the *Z*-configuration of the acrylonitrile residue. Such isomers are generally the more soluble and remain in solution on recrystallisation.

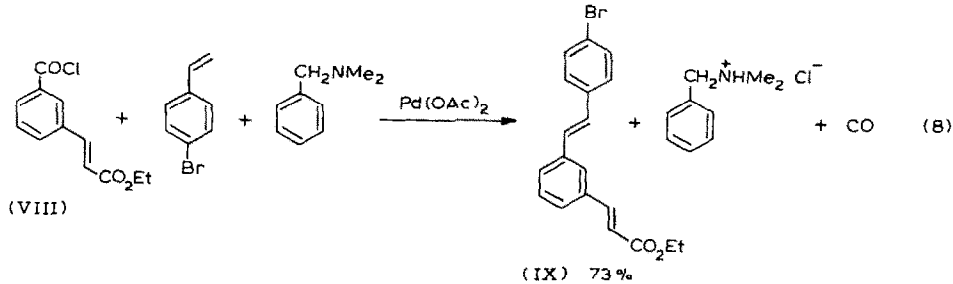
The above results show that 1,4-divinylbenzene derivatives are best prepared by carrying out the first arylation with the aroyl chloride. This is because of the unfavourable substituent effect of the 4-vinyl group (see below). This does not appear to be the case for a 3-vinyl substituent.

3-Bromobenzoic acid reacted with ethyl acrylate to give (*E*)-ethyl 3-hydroxycarbonylcinnamate (VII) in 81% yield (eq. 7).



(VII) 81%

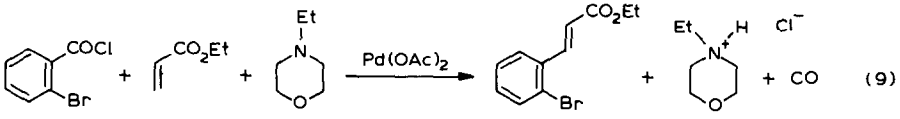
VII was converted with thionyl chloride to (*E*)-ethyl 3-chlorocarbonylcinnamate (VIII) in 91% yield. This reacted with 4-bromostyrene to give (*E*,*E*)-4-bromo-3′-(2-ethoxycarbonylvinyl)stilbene (IX) in 73% yield (eq. 8), giving an overall yield of 54% over three stages. Further arylation via the bromine atom of IX is possible.



(VIII) (IX) 73%

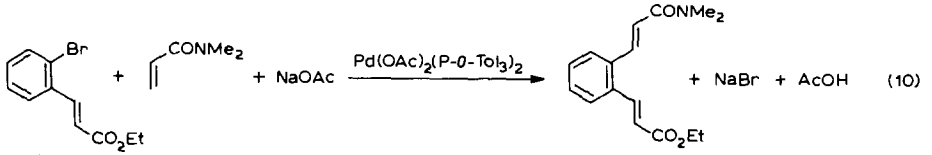
2-Bromobenzoic acid has been said not to react in the arylation reaction unless the carboxylate group is esterified [4]. To avoid the extra steps involved it was

converted to 2-bromobenzoyl chloride (X) with thionyl chloride, the yield being 96%. X gave (*E*)-ethyl 2-bromocinnamate (XI) in 61% yield on reaction with ethyl acrylate (eq. 9). *N*-Ethylmorpholine as base gave better results than *N*-benzyldimethylamine in this case [1].



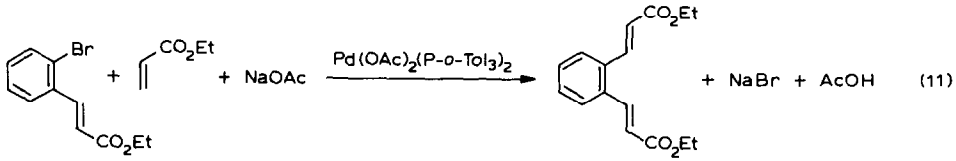
(X) (XI) 61%

XI reacted with *N*,*N*-dimethylacrylamide to give (*E*,*E*)-1-(2-ethoxycarbonylvinyl)-2-[2-(*N*,*N*-dimethylcarbamoyl)vinyl]benzene (XII) in 90% yield (eq. 10). The yield over three stages is here 53%.



(XI) (XII) 90%

XI also reacted with a second mole of ethyl acrylate to give (*E*,*E*)-1,2-bis(2-ethoxycarbonylvinyl)benzene (XIII) in a yield of 87% (eq. 11).



(XI) (XIII) 87%

This is a yield over three stages of 51%. Interestingly, attempts to make XIII directly from two moles of ethyl acrylate and either phthaloyl chloride or 1,2-dibromobenzene were unsuccessful. When phthaloyl chloride was used, this reacted rapidly with the base to give unidentified products. The ethyl acrylate remained unreacted. *N*-Benzyldimethylamine, *N*-ethylmorpholine and tri-(n-butyl)amine were all tried as bases, without success. 1,2-Dibromobenzene gave no catalytic reaction at all, regardless of whether palladium acetate was used alone as catalyst, or in conjunction with triphenylphosphine or tri(*o*-tolyl)phosphine. Conceivably, after the oxidative addition of one C–Br bond to palladium(0) the interaction of the other bromine atom with the resulting palladium(II) complex is strong enough to prevent alkene insertion from taking place. It should however be noted that reaction 9 proceeds readily, although a similar intermediate must occur after the decarbonylation step.

The results show that 1,2-, 1,3- and 1,4-substituted divinylbenzene derivatives can be readily prepared by this method. In arylation with aroyl chlorides, the best results have generally been obtained with *N*-benzyldimethylamine as base, but where this gives low yields (e.g. reaction 9) *N*-ethylmorpholine should be tried [1]. Arylation with aryl bromides generally proceeded best with tri(*o*-tolyl)-phosphine as ligand [2,5] but the ratio of ligand to palladium is important (see reaction 7). A ratio of two was generally used. Where results with tri(*o*-tolyl)phosphine are unsatisfactory,

triphenylphosphine should be tried. Aryl bromides having strongly electron-withdrawing substituents may react better when palladium acetate is used without a phosphorus ligand [2].

In the preparation of 1,4-divinylbenzene derivatives, the best results have been obtained when carrying out the first arylation with the aroyl chloride. If the first step involves the aryl bromide, the aroyl chloride used in the second arylation necessarily has a vinyl substituent in the 4-position. We have generally found that such aroyl chlorides give poorer results than those having a 4-bromo substituent. In the case of 1,3-derivatives, this may not necessarily be the case. Thus reaction 8 gave a yield of 73%. Since 2-bromobenzoic acid does not react as an aryl bromide unless esterified, the first arylation here is best carried out with the aroyl chloride.

Experimental

Palladium acetate was obtained from Engelhard. Tri(*o*-tolyl)phosphine was prepared by the literature method [5]. Other chemicals were from Fluka, EGA or Merck. Activated alkenes were used as received. *N*-Benzyldimethylamine and *N*-ethylmorpholine were freshly distilled from potassium hydroxide. The sodium acetate used was anhydrous. ^{1}H NMR spectra (250 MHz) were recorded with a Bruker WM 250; IR spectra with Varian 157 and 298; and mass spectra with Varian CH 5 and CH 7 instruments. Elemental analyses were performed by the Microanalytical Laboratory at Ciba-Geigy. Yields quoted are of the pure isolated product. Reactions were carried out in a normal reflux apparatus. All palladium-catalysed reactions were carried out under argon.

Preparation of 4-bromobenzoyl chloride (I)

To 4-bromobenzoic acid (100.5 g, 0.5 mol) were added thionyl chloride (43.6 ml, 0.6 mol), toluene (255 ml) and *N*,*N*-dimethylformamide (0.07 ml). The mixture was stirred for 2 h at 60°C and then 1 h at 70°C with exclusion of moisture. Toluene and excess thionyl chloride were removed on a rotary evaporator and the product was distilled under vacuum (78–83°C/0.2 mmHg). Yield 103.9 g (95%). Colourless liquid, setting rapidly to a white solid, m.p. 35.5–35.8°C. Anal. Found: C, 38.71; H, 2.04; Br, 35.96; Cl, 16.02; O, 7.24. C_7H_4BrClO calcd.: C, 38.27; H, 1.82; Br, 36.45; Cl, 16.17; O, 7.29%.

Preparation of (E)-ethyl 4-bromocinnamic acid (II)

To *p*-xylene (200 ml) were added palladium acetate (0.02244 g, 0.1 mmol), I (21.95 g, 0.1 mol), ethyl acrylate (10.83 ml, 0.1 mol) and *N*-benzyldimethylamine (15.06 ml, 0.1 mol). The mixture was stirred for 1 h at 130°C. At room temperature it was filtered and the precipitate was washed with toluene (50 ml). This gave nearly pure *N*-benzyldimethylammonium chloride (15.74 g, 92%) from which the base can be readily recovered. The combined filtrates were extracted with 2 *N* hydrochloric acid (50 ml), 2 *N* aqueous sodium hydroxide (50 ml) and water (50 ml). After drying with $MgSO_4$ (10 g) for 15 min, the solvents were removed on the rotary evaporator and the crude product was fractionally distilled in vacuum (130–135°C/0.2 mmHg). Yield 20.1 g (79%). Colourless liquid. Anal. Found: C, 52.07; H, 4.50; Br, 31.01. $C_{11}H_{11}BrO_2$ calcd.: C, 51.79; H, 4.35; Br, 31.32%.

Preparation of (E,E)-1-(2-ethoxycarbonylvinyl)-4-(2-cyanovinyl)benzene (III)

To DMF (25 ml) were added diacetatobis[tri(*o*-tolyl)phosphine]palladium(II)

(0.0208 g, 0.025 mmol), II (4.66 ml, 25 mmol), acrylonitrile (1.83 ml, 27.5 mmol) and sodium acetate (2.26 g, 27.5 mmol). The mixture was stirred at 130°C for 3.5 h. At room temperature it was poured into water (100 ml). The product was extracted with dichloromethane (50 and 25 ml). After drying with $MgSO_4$ (7.5 g) for 15 min and removal of the solvents the crude product was recrystallised from methanol (25 ml), with cooling in ice. Yield 3.79 g (67%). Light brown crystals, m.p. 121–122°C. Anal. Found, C, 74.12; H, 6.02; N, 6.45; O, 14.03. $C_{14}H_{13}NO_3$ calcd.: C, 73.99; H, 5.77; N, 6.16; O, 14.08%.

III was also prepared from V and from VI by analogous procedures.

Preparation of (E)-ethyl 4-hydoxycarbonylcinnamate (IV)

This was prepared by a method analogous to that for III using DMF (100 ml), diacetatobis[tri(*o*-tolyl)phosphine]palladium(II) (0.0832 g, 0.1 mmol), 4-bromobenzoic acid (20.1 g, 0.1 mol), ethyl acrylate (11.92 ml, 0.11 mol) and sodium acetate (9.02 g, 0.11 mol) at 130°C for 2 h. Water (200 ml) was added to the reaction mixture which was then poured into 2 *N* hydrochloric acid (200 ml). The product was extracted with dichloromethane (200 and 100 ml) dried for 15 min with $MgSO_4$ (35 g) and the solvents were removed on the rotary evaporator. The crude product was recrystallised from toluene (25 ml) and dried at 60°C in vacuum. Yield 17.44 g (79%). White crystals, m.p. 196–197°C. Anal. Found: C, 65.20; H, 5.48; O, 29.43. $C_{12}H_{12}O_4$ calcd.: C, 65.45; H, 5.50; O, 29.06%.

Preparation of (E)-ethyl 4-chlorocarbonylcinnamate (V)

IV (14 g, 63.4 mmol), thionyl chloride (5.5 ml, 75.7 mmol), toluene (100 ml) and DMF (0.18 ml) were refluxed for 40 min with exclusion of moisture. After concentration on the rotary evaporator the solid residue was recrystallised from n-hexane (80 ml). Yield 12.13 g (88%). White crystals, m.p. 77°C. Anal. Found: C, 60.25; H, 4.95; Cl, 15.08. $C_{12}H_{11}ClO_3$ calcd.: C, 60.39; H, 4.65; Cl, 14.85%.

Preparation of 4-bromocinnamonitrile (VI)

This was prepared as described for II using *p*-xylene (200 ml), palladium acetate (0.02244 g, 0.1 mmol), I (21.95 g, 0.1 mol), acrylonitrile (6.66 ml, 0.1 mol) and *N*-benzyldimethylamine (15.06 ml, 0.1 mol). The mixture began to reflux at 124°C, and slowly reached 130°C, where it was maintained, as the alkene was consumed. The total reaction time was 2.5 h. After removal of the *N*-benzyldimethylammonium chloride (15.36 g, 90%) and work up as for II, the crude product was distilled in vacuum. Yield 14.51 g (70%). Colourless liquid rapidly setting to a white solid which is 91% *E*- and 9% *Z*-isomer, m.p. 102.5–103.5°C. Anal. Found: C, 51.93; H, 3.01; N, 6.69; Br, 38.35. C_9H_6NBr calcd.: C, 51.96; H, 2.91; N, 6.73; Br, 38.40%.

Preparation of (E)-ethyl 3-hydroxycarbonylcinnamate (VII)

This was prepared as described for III using DMF (25 ml), diacetatobis[tri(*o*-tolyl)phosphine]palladium(II) (0.0208 g, 0.025 mmol), tri(*o*-tolyl)phosphine (0.0152 g, 0.05 mmol) 3-bromobenzoic acid (5.03 g, 25 mmol), ethyl acrylate (2.98 ml, 27.5 mmol) and sodium acetate (2.26 g, 27.5 mmol). After 5 h at 130°C and work up as for IV the crude product was recrystallised from toluene (15 ml). Yield 4.45 g (81%). White crystals, m.p. 159°C. Anal. Found: C, 65.45; H, 5.32; O, 28.93. $C_{12}H_{12}O_4$ calcd.: C, 65.45; H, 5.50; O, 29.06%.

Preparation of (E)-ethyl 3-chlorocarbonylcinnamate (VIII)

VII (5.5 g, 25 mmol), thionyl chloride (2.18 ml, 30 mmol), toluene (20 ml) and DMF (0.01 ml) were stirred for 1.5 h at 70°C with exclusion of moisture. After removal of toluene and thionyl chloride on the rotary evaporator the crude product was distilled in vacuum (155–160°C/0.2 mmHg). Yield 5.48 g (92%). Colourless liquid. Anal. Found: C, 60.19; H, 4.67; Cl, 15.27; O, 20.04. $C_{12}H_{11}ClO_3$ calcd.: C, 60.39; H, 4.65; Cl, 14.85; O, 20.11%.

Preparation of (E,E)-4-bromo-3'-(2-ethoxycarbonylvinyl)stilbene (IX)

This was prepared as described for II using *p*-xylene (50 ml), palladium acetate (0.00561 g, 0.025 mmol), VIII (5.96 g, 25 mmol) 4-bromostyrene (2.87 ml, 25 mmol) and *N*-benzyldimethylamine (3.76 ml, 25 mmol). After 2 h at 130°C and work up as for II the crude product was recrystallised from 2-propanol (30 ml). Yield 6.54 g (73%). White crystals, m.p. 100–101°C. Anal. Found: C, 63.81; H, 4.86; O, 8.99; Br, 22.15. $C_{19}H_{17}BrO_2$ calcd.: C, 63.88; H, 4.80; O, 8.96; Br, 22.37%.

Preparation of 2-bromobenzoyl chloride (X)

To 2-bromobenzoic acid (293.8 g, 1.45 mol) were added thionyl chloride (128 ml, 1.75 mol), toluene (400 ml) and DMF (0.3 ml). The mixture was stirred for 2 h at 40°C and then 1 h at 60°C with exclusion of moisture. Toluene and excess thionyl chloride were removed on the rotary evaporator and the product was distilled under vacuum (117–118°C/ 12 mmHg). Yield 304.1 g (96%). Colourless liquid. Anal. Found: C, 38.15; H, 1.87; Cl, 16.07; Br, 36.55; O, 7.71. C_7H_4BrClO calcd.: C, 38.31; H, 1.84; Cl, 16.15; Br, 36.41; O, 7.29%.

Preparation of (E)-ethyl 2-bromocinnamate (XI)

This was prepared as described for II using *p*-xylene (400 ml), palladium acetate (0.04488 g, 0.2 mmol), X (43.90 g, 0.2 mol), ethyl acrylate (21.67 ml, 0.2 mol) and *N*-ethylmorpholine (25.23 ml, 0.2 mol). After 9 h at 130°C and work up as for II (*N*-ethylmorpholinium chloride 28.79 g, 95%), the crude XI was distilled under vacuum (110–112°C/ 0.55 mmHg) Yield 31.2 g (61%). Colourless liquid. Anal. Found: C, 51.97; H, 4.45; O, 13.05; Br, 30.59. $C_{11}H_{11}BrO_2$ calcd.: C, 51.79; H, 4.35; O, 12.54; Br, 31.32%.

Preparation of (E'E)-1-(2-ethoxycarbonylvinyl)-2-[2-(N,N-dimethylcarbamoyl)vinyl]-benzene (XII)

This was prepared as described for III using DMF (25 ml), diacetatobis[tri(*o*-tolyl)phosphine]palladium(II) (0.0208 g, 0.025 mmol), XI (6.38 g, 25 mmol), *N*,*N*-dimethylacrylamide (2.75 g, 27.5 mmol) and sodium acetate (2.26 g, 27.5 mmol). After 4.5 h at 130°C and work up as for III, the crude product was chromatographed on a short Kieselgel 60 column in ethyl acetate and distilled in vacuum (194–197°C/0.2 mmHg). Yield 6.11 g (90%). Yellow oil, which crystallised on standing. Anal. Found: C, 70.06; H, 7.28; N, 5.00; O, 17.94. $C_{16}H_{19}NO_3$ calcd.: C, 70.31; H, 7.01; N, 5.13; O, 17.56.

Preparation of (E,E)-1,2-bis(2-ethoxycarbonylvinyl)benzene (XIII)

This was prepared as described for III using DMF (25 ml), diacetatobis[tri(*o*-tolyl)phosphine]palladium(II) (0.0208 g, 0.025 mmol), XI (6.38 g, 25 mmol), ethyl

acrylate (2.98 ml, 27.5 mmol) and sodium acetate (2.26 g, 27.5 mmol). After 6 h at 130°C and work up as for III, the crude product was recrystallised from n-hexane (15 ml). Yield 5.94 g (87%). Yellow crystals, m.p. 74°C. Anal. Found: C, 69.74; H, 6.97; O, 23.41. $C_{16}H_{18}O_4$ calcd.: C, 70.06; H, 6.62; O, 23.33%.

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