The Effect of the Carbon Ligand on the Reaction of Organozinc Reagents in the Synthesis of Substituted 2,5-Dihydrofurans: A Rare Example of An Uncatalysed Allylic-Substitution Reaction Involving Alkyl Zinc Halides

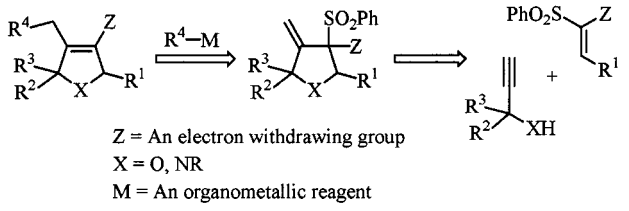
Mark Woods,[a] Nuno Monteiro,[a] and Geneviève Balme*[a]

Keywords: Heterocycles / Zinc / Palladium / Catalysts / Sulfur

Organozinc halides derived from Grignard reagents behave differently in their reaction with ethyl (±)-(2*RS*,3*SR*)-tetrahydro-4-methylene-2-phenyl-3-(phenylsulfonyl)furan-3-carboxylate (**3**) according to the hybridisation of the carbon ligand. During the development of short multi-component reactions for the synthesis of diverse functionalized ethyl 2,5-dihydrofuran-3-carboxylates it was discovered that aryl and vinyl zinc halides undergo clean reaction with **3** in the presence of $Pd(PPh_3)_4$. In contrast, when alkyl zinc halides are reacted with **3** in the presence of $Pd(PPh_3)_4$, reductive desulfonation of **3** is observed. Remarkably, in the absence of a transition metal catalyst, the allylic substitution of **3** with alkyl zinc halides proceeds cleanly and in moderate to good yield.

Introduction

The use of combinatorial chemistry in the synthesis of compound libraries and, in particular, those containing heterocyclic motifs is of growing importance in drug discovery research. For this purpose it is advantageous to use short synthetic routes in which the maximum number of substituents can be varied with the minimum of effort. One- or two-step, multi-component reactions in which no functional group protections are necessary are therefore at a premium.[1] Previous work has shown that five-membered heterocyclic compounds may be synthesised from propargyl alcohol or amine and an appropriate Michael acceptor.[2] The introduction of a third component into this synthesis would greatly enhance the diversity of products available,[3] hence a three-component synthesis of substituted 2,5-dihydrofurans was postulated (Scheme 1).



Scheme 1. Multi-component reactions allow the facile introduction of a wide range of substituents

The inclusion of the phenyl sulfone moiety in the compound is central to the synthetic strategy. Sulfone groups are known to impart diverse chemical properties upon organic compounds.[4] In this case the phenyl sulfone first acts as one of the electron-withdrawing groups, stabilising the anionic intermediate during the cyclisation reaction. The sulfone may then act as a leaving group in the cyclised product **3** allowing further functionalisation of the heterocycle by allylic substitution. The tolerance of most functional groups by organozinc reagents makes them ideal candidates in this context.

Over the past two decades the use of organozinc reagents in organic synthesis has become commonplace.[5] Like their copper(I) counterparts[6] they offer a milder reagent with greater chemoselectivity than the corresponding lithiates or Grignard reagents. However, most organozinc reagents are relatively unreactive and direct reactions with carbon electrophiles are rare and almost exclusively restricted to allylic zinc reagents.[5b] In general, reactions of organozinc reagents require catalysis, more usually with Pd^0, Pd^{II}, Ni^0, Ni^{II} or Cu^I [5] but Co^{II}, Mn^{II} and Fe^{III} have also been employed for the purpose.[5b][5c] Organozinc reagents may be divided into two distinct types: diorganozincs and the more reactive organozinc halides. It is with the latter that this paper is concerned.

Organozinc halides may be prepared in a number of ways: by transmetallation (usually of a lithiate or Grignard reagent),[7] by electrochemical methods,[8] or by oxidative addition of an organic bromide or iodide to activated zinc.[9] This latter method offers the advantage that almost all functional groups may be included in the organozinc halide.

The synthesis and subsequent substitution reactions of organozinc halides with ethyl tetrahydro-2-phenyl-3-(phenylsulfonyl)-4-methylenefuran-3-carboxylate **(3)** have been investigated with this aim.

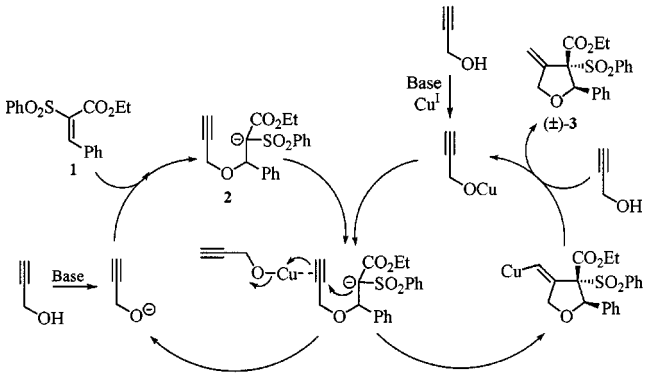
Results and Discussion

Ethyl tetrahydro-2-phenyl-3-(phenylsulfonyl)-4-methylenefuran-3-carboxylate **(3)** was synthesised using methods

[a] Laboratoire de Chimie Organique 1, Associé au CNRS,
Université Claude Bernard Lyon 1, CPE,
43 Boulevard du 11 Novembre 1918,
69622 Villeurbanne, France
Fax: (internat.) + 33-47/243-1214
E-mail: balme@univ-lyon1.fr

  1434–193X/00/0509–1711 $ 17.50+.50/0

recently reported for the synthesis of a range of 4-methylene tetrahydrofurans[2a] and pyrrolidines.[2b] The Michael addition of propargyl alcohol to ethyl 2-phenylsulfonyl cinnamate **(1)**,[10] in THF, may be catalysed by sodium hydride to generate the stabilised anionic intermediate **2**. Cyclization is then mediated by catalytic quantities of an appropriate Pd^0 complex[2a] or, in a new departure, a Cu^I complex.[2b] Coordination to Cu^I activates the triple bond to nucleophilic attack and protonation of the vinyl copper intermediate by propargyl alcohol regenerates the Cu^I catalyst and affords the cyclized 4-methylene tetrahydrofuran **3** (Scheme 2). Although $Pd(OAc)_2(PPh_3)_n$ (n = 1–2) is highly effective in the catalysis of this cyclization (90%), for the preparation of bulk quantities of **3** the use of $CuI(PPh_3)_n$ complexes (n = 1–3) was preferred for economic reasons. These complexes may be prepared beforehand[11] but are just as effective when prepared in situ and they offer the advantage over CuI of increased solubility in organic solvents.



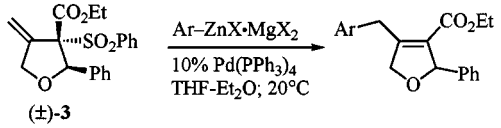
Scheme 2. Cu(I) catalysed synthesis of the allylic sulfone **3**

In common with related tetrahydrofurans synthesised in this way[2a] ^1H and ^{13}C NMR spectroscopy revealed that the 4-methylene tetrahydrofuran **3** is formed as a single diastereoisomer. In view of the likely steric interactions between the phenyl group in the 2-position and the phenyl sulfone, it was expected that this would be the (2*RS*, 3*SR*)-isomer which allows the phenyl and phenyl sulfone groups to adopt a *trans* relationship and thereby minimise steric interaction. This assignment is supported by comparison of the ^1H NMR shift of the methyl group of the carboxy ethyl ester in this and related compounds.[2a] The resonance of the methyl group in compound **3** exhibits an upfield shift of about 0.6 ppm (δ_H = 0.79) consistent with a *cis* relationship with the α-phenyl group. A *cis* relationship would result in shielding of the methyl resonance by the phenyl group displacing the resonance upfield.

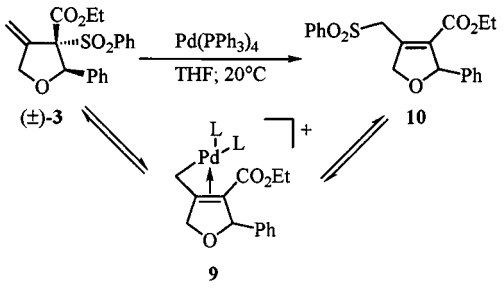
Allylic sulfones are known to oxidatively add to Pd^0 to form Pd^{II} π-allyl complexes. These complexes may then be attacked by a wide range of nucleophilic reagents. In principle a Pd^{II} π-allyl complex may be attacked at either end; however, the least-substituted end is usually attacked preferentially. Additionally, the presence of carboxyesters at one terminus of the π-allyl complex is known to direct attack to the opposite end of the allylic system.[12] Hence, in this case, attack would be expected to occur solely at the methylene carbon, the γ-position.

The reactivity of aryl zinc halides with Pd^{II} π-allyl complexes[7,13] and other Pd complexes[14] has been demonstrated. Indeed aryl zinc halides have recently been shown to react with allylic sulfones in the presence of catalytic quantities of $Pd(PPh_3)_4$.[7a] Accordingly, phenyl zinc chloride was prepared by transmetallation of the corresponding Grignard reagent. Phenyl magnesium bromide was added slowly to a solution of zinc chloride in Et_2O and THF. Upon formation of the organozinc halide the precipitation of a white solid from the reaction medium is observed. This is in contrast to organozinc halides prepared using the methods of Rieke and co-workers[8] which remain in solution. It is reasonable to assume that, as with their copper(I) counterparts, the presence of magnesium salts is important to the reactivity of organozincs prepared in this way.[6] Indeed magnesium salts have been shown to promote the reactions of other organometallic reagents, presumably due to their Lewis acidity.[15] For this reason organozinc halides are herein described by an empirical formula taking the salts into account.

The allylic substrate **3** and 10% $Pd(PPh_3)_4$ were added to a suspension of four equivalents of phenyl zinc chloride. After 18 h at room temperature complete consumption of the starting material **3** was observed by TLC analysis. After purification by column chromatography the 4-benzyl-2,5-dihydrofuran **4** was obtained in 63% yield (Scheme 3). The reaction was found to be tolerant of both electron-withdrawing, such as *o*-CF_3, and electron-donating groups, such as *p*-$N(Me)_2$ (Table 1).



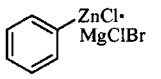
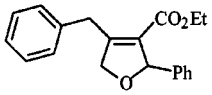
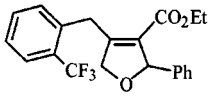
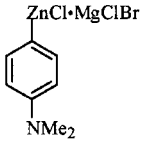
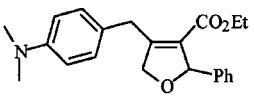
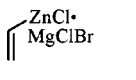
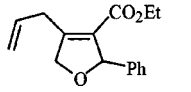
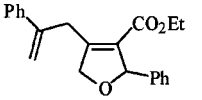
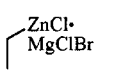
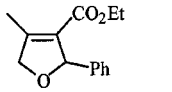
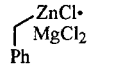
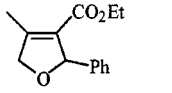
Scheme 3. Aryl zinc halides react with **3** in the presence of catalytic quantities of $Pd(PPh_3)_4$



Scheme 4. Pd^0 catalysed rearrangement of the allylic sulfone **3**

Vinyl zinc halides also proved to be effective nucleophiles under these conditions (Table 1). In the absence of Pd^0 no reaction was observed with either aryl or vinyl zinc chlorides, consistent with the involvement of the Pd^{II} π-allyl complex **9**. When the 4-methylene tetrahydrofuran **3** is treated with catalytic quantities of $Pd(PPh_3)_4$ in THF at room temperature in the absence of a nucleophile, the phenyl sulfone group is displaced from the α- to the γ-position (Scheme 4). This displacement is known to occur via

Table 1. Palladium-catalysed reaction of **3** with aryl and vinyl zinc halides

Organozinc	Time	Product		Yield
	18h		**4**	63%
	18h		**5**	81%
	18h		**6**	61%
	18h		**7**	72%
	18h		**8**	85%
	18h		**13**	56%
	18h		**13**	68%

formation of a Pd^{II} π-allyl complex[16] and results in the formation of the regioisomeric 2,5-dihydrofuran **10**.

Changing the carbon ligand on zinc from an sp^2 to an sp^3 hybridised carbon results in a drastic change in the course of the reaction. When ethyl zinc chloride, prepared from ethyl magnesium bromide, is reacted with **3** under the same reaction conditions employed for aryl zinc halides, only traces of the substitution product **15** were observed. The major reaction product was **13** arising from reductive desulfonation of the allylic sulfone.

The reduction of substrates during palladium-catalysed reactions is well known;[17–19] however, only one instance of alkyl zinc halides and Pd^0 reducing allylic substrates has been reported.[18] The hydrogen source in this case was assumed to be β-hydride transfer from the alkyl zinc reagent. Such a mechanism would suggest that if an sp^3 hybridised organozinc halide without β-hydrogens, such as benzyl zinc chloride, were used then no reductive desulfonation would occur. In contrast, when benzyl zinc chloride was employed the reduced product **13** was the sole reaction product, implying that the organozinc reagent is *not* the hydrogen source.

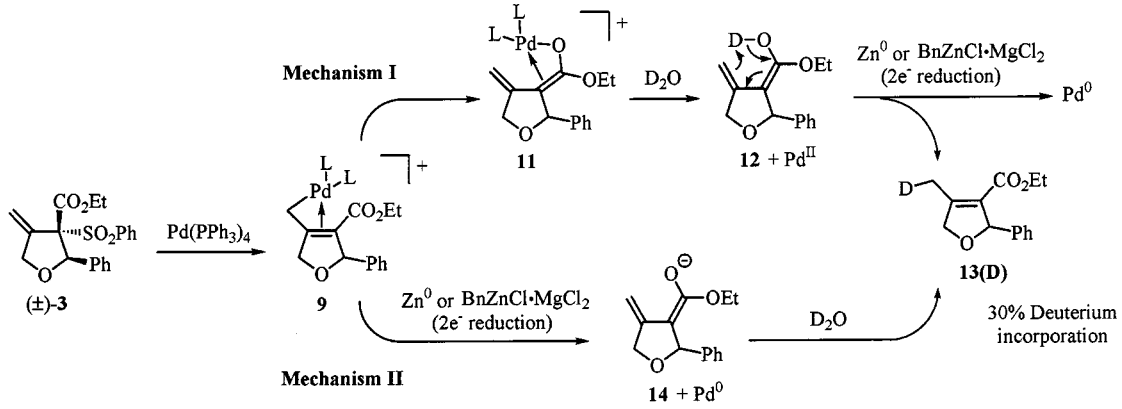
An alternative source of hydrogen, as has already been suggested in the reduction of Pd complexes,[17a] could be traces of water in the reaction medium. Only around 0.1% water in the reaction medium would be sufficient to provide one equivalent of hydrogen. To investigate this possibility 1.3 equivalents of D_2O were added to the reaction with benzyl zinc chloride. The incorporation of deuterium in the 4-methyl-2,5-dihydrofuran **13** was confirmed by ^1H NMR and mass spectrometry, with around 30% incorporation being observed exclusively in the 4-methyl position. When D_2O was added to the same reaction with ethyl zinc chloride deuterium incorporation was also observed. It is worthy to note that the same reduction products are observed when activated Zn^0 is substituted for the organozinc reagent.

Two mechanisms have been proposed for analogous reductions involving palladium intermediates, both of which may apply in this case (Scheme 5). It has been suggested that Pd^{II} π-allyl complexes in the presence of a suitably positioned carbonyl group may migrate to form a Pd^{II} enolate complex **11**.[17] Hydrolysis of such a complex would lead to the dienol **12**, which would be expected to undergo a rapid six-electron tautomerisation to afford the reduced product **13** (Scheme 5, Mechanism I). The catalytic cycle of palladium is completed by the reduction of the Pd^{II} to Pd^0 by the alkyl zinc reagent or zinc metal.

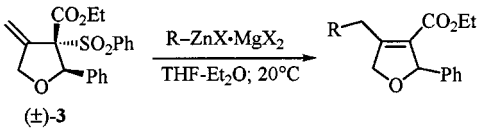
The second mechanism involves the alkyl zinc halide acting as a two-electron reductant, a feat of which it seems aryl and vinyl zinc halides are incapable. The Pd^{II} π-allyl complex **9** is reduced by two-electron transfer from the alkyl zinc halide or Zn^0 affording the anionic species **14**, (Scheme 5, Mechanism II).[19] Quenching of dienolate **14** by residual water would complete the reductive desulfonation and regenerate the Pd^0 catalyst. In principle either or both of these mechanisms are viable. The reported reduction by Pd^0 and alkyl zinc reagents of allylic systems in which there is no proximate carbonyl group[18] may suggest that the latter mechanism seems the more probable; however, neither may reasonably be discounted.[20]

Alkyl substitution of **3** may be effected by the unusual but simple expedient of omitting the palladium catalyst. When **3** was added to four equivalents of ethyl zinc chloride in THF or Et_2O the allylic substitution proceeded with complete regio- and chemoselectivity in 18 h at room temperature (Scheme 6). The 4-propyl-substituted 2,5-dihydrofuran **15** was obtained in 86% yield. This reaction was extended to other alkyl zinc halides with yields varying from moderate to good (Table 2). When benzyl or allylic zinc chlorides were employed, however, the starting material **3** remained unchanged. The failure of the allylic zinc chlorides to react is remarkable in the light of the fact that most reported uncatalysed reactions of organozincs involve allylic zinc reagents.[5b] The low reactivity of these latter three organozinc halides may be ascribed to the delocalisation of the negative charge in these reagents.

To establish the extent to which the uncatalysed reaction of alkyl zinc halides with allylic sulfones is a general phenomenon compounds **20–22** (Figure 1) were treated with ethyl or cyclohexyl zinc chlorides under the conditions described previously. In each case the starting sulfone was recovered in quantitative yield. Strain arising from accommodating a carboxy ethyl ester and a phenyl sulfone on the same carbon atom may labilise the sulfone **3** to allylic at-

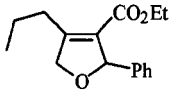
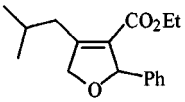
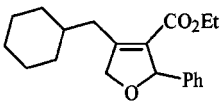
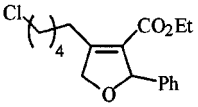
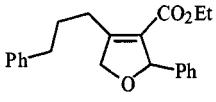


Scheme 5. Reductive desulfonation of **3** may proceed by hydrolysis of a Pd^{II} enolate complex or through an allylic anion



Scheme 6. Alkyl substitution of **3** proceeds in the absence of catalyst

Table 2. Uncatalysed reaction of **3** with alkyl zinc halides

Organozinc	Time	Product		Yield
ZnCl· MgClBr	18h		**15**	86%
ZnCl· MgClBr	18h		**16**	61%
ZnCl· MgClBr	18h		**17**	71%
Cl(CH2)3 ZnCl· MgClBr	18h		**18**	42%
Ph ZnCl· MgClBr	48h		**19**	35%
Ph ZnCl· MgCl2	48h	No reaction		
ZnCl· MgClBr	48h	No reaction		
ZnCl· MgClBr	48h	No reaction		

tack. In addition, the energy gain in conjugating the double bond to the ester in the 2,5-dihydrofuran products is likely to further favour the expulsion of the phenyl sulfone group.

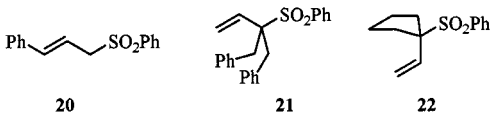


Figure 1

In this respect the allylic sulfone **3** seems to be the exception rather than the rule.

Three distinct types of organozinc halide emerge from these results, each possessing very different reactivities from the others. Consequently care must be taken when attempting these allylic substitutions to ensure that appropriate conditions are chosen for the particular organozinc halide employed. The reactivity of organozinc halide reagents is apparently related to the hybridisation of the carbon ligand. Alkyl zinc halides where the negative charge is centred in an sp^3 hybridised orbital are more reactive nucleophiles. They are reactive enough to substitute the allylic sulfone **3** without requiring transition metal catalysis. Where the negative charge can be delocalised into an adjacent π-system this reactivity is diminished. Neither benzyl nor allyl zinc halides, nor the sp^2 hybridised aryl or vinyl zinc halides, are sufficiently reactive to substitute **3** without transition metal catalysis. Aryl and vinyl zinc halides are, however, reactive towards Pd^{II} π-allyl complexes.

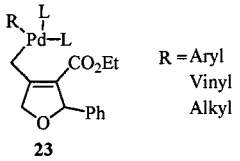


Figure 2

Organozinc reagents are known to transmetalate cationic Pd^{II} π-allyl complexes to form neutral complexes, e.g. **23** (Figure 2).[13] Cross-coupling then occurs via reductive elimination of the two organic ligands from **23**. Reductive elimination is favoured when sp^2-hybridised ligands are involved.[5c] Thus, when aryl or vinyl zinc halides are employed, reductive elimination is fast affording the corresponding substituted product. Reductive elimination involving two sp^3-hybridised ligands is usually much slower as a result of increased electron density at the metal centre.[5c]

The result is that when benzyl, allyl or alkyl zinc halides are employed the rate of cross-coupling is slow and competing reductive desulfonation mechanisms dominate the reaction.

Aryl, vinyl and alkyl zinc halides all exhibited complete chemo- and regioselectivity in their reactions with **3**. Allylic substitution of the phenyl sulfone was the sole reaction and proceeded with substitution exclusively at the least-hindered γ-terminus in all cases.

Conclusions

An effective two-step synthesis of substituted ethyl 2,5-dihydrofuran-3-carboxylates has been developed in which the substituent in the 4-position may be varied multifariously. Further diversification may now be effected by variation of the substituents of the two components involved in the cyclization step and application of this synthesis to the solid phase. The results of reaction between organozinc halides and the intermediate **3** were found to be highly dependent upon the hybridisation of the carbon ligand on zinc. The often-problematic reaction of alkyl zinc halides was found to proceed cleanly and, unusually, in the absence of a transition metal catalyst.

Experimental Section

Where available all Grignard reagents were purchased from the Sigma-Aldrich company. In all other cases they were prepared from the corresponding bromide and magnesium in tetrahydrofuran. All Grignard reagents were standardised using the Watson and Eastham charge-transfer method.[21] Freshly distilled THF dried over sodium/potassium alloy with benzophenone indicator was used throughout. Petroleum ether refers to the 40–65°C fraction of petroleum ether. All reactions were carried out under nitrogen.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300X operating at 300.1 MHz and 75.5 MHz, respectively. Chemical shift values are quoted in ppm; *J* values are given in Hz. Mass spectra were recorded on a Nermag R10–10H spectrometer. Gas chromatography was performed on a Varian 3300 using a 30m DB5 column and a temperature ramp of 10 °C min^{-1} from 220–280°C. Infrared spectra were recorded on a Perkin–Elmer 298 CW spectrophotometer.

Ethyl (±)-(2*RS*,3*SR*)-Tetrahydro-4-methylene-2-phenyl-3-(phenylsulfonyl)furan-3-carboxylate (3): Propargyl alcohol (0.71 g, 12.60 mmol) was added dropwise to a suspension of sodium hydride (0.13 mg, 3.20 mmol) in tetrahydrofuran (3 mL). The yellow solution was left to stir for 5 min and ethyl 2-phenylsulfonyl cinnamate **(1)** (2.00 g, 6.30 mmol) added. After a further 5 min of stirring CuI(PPh$_3$)$_3$ (1.85 g, 1.90 mmol) was added and the reaction left to stir overnight. The reaction mixture was filtered through a plug of silica gel eluting with ethanol. The residue was crystallised from CH_2Cl_2 and ethanol then from Et_2O and petroleum ether affording the title compound as a colourless solid (2.00 g, 86%), m.p. 121–122°C. – R_f = 0.2 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 8.6 min. – $C_{18}H_{20}SO_5$ (348.4): calcd. C 64.5, H 5.4; found C 64.1, H 5.3. – $\tilde{\nu}_{max}$ = 3085 cm^{-1}, 3061, 3032, 2980, 2919, 2863, 1736 (CO), 1582, 1447, 1367, 1308 (SO_2), 1234, 1143 (SO_2), 1079, 1058, 1026, 962, 914, 849, 766, 754, 738, 719. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.04 (dd, ^3J = 6, ^4J = 1 Hz, 2 H, ArH-2), 7.70 (tt, ^3J = 7, ^4J = 1 Hz, 1 H, ArH-4), 7.56 (dd, ^3J = 6, ^3J = 7 Hz, 2 H, ArH-3), 7.30 (m, 5 H, Ph), 5.90 (s, 1 H, H-2), 5.54 (dd, ^2J = 2, ^4J = 2 Hz, 1 H, =CH), 5.51 (dd, ^2J = 2, ^4J = 3 Hz, 1 H, =CH), 4.65 (dt, ^2J = 13, ^4J = 2 Hz, 1 H, H-5$_a$), 4.28 (dt, ^2J = 13, ^4J = 3 Hz, 1 H, H-5$_b$), 3.68 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 3.67 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 0.79 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.2 (OCH$_2$*C*H$_3$), 62.2 (O*C*H$_2$CH$_3$), 72.4 (C-4), 84.9 (C-3), 85.3 (C-2), 115.9 (=CH$_2$), 127.2 (ArC), 128.2 (ArC), 128.5 (ArC), 128.6 (ArC), 128.8 (ArC), 132.0 (ArC), 134.4 (ArC), 137.4 (C-4), 141.5 (ArC-1′), 164.4 (CO). – EI-MS: *m*/*z* (%) = 231 (60) [M – SO_2Ph]$^+$, 185 (93) [M – OEt, – SO_2Ph]$^+$, 158 (27) [M – CO_2Et – SO_2Ph]$^+$, 105 (37) [PhCO$^+$], 77 (100) [Ph$^+$].

General Method for the Synthesis of Ethyl 4-Benzyl-2,5-dihydro-2-phenyl-(or -allyl-)furan-3-carboxylates: Ethyl (±)-4-Benzyl-2,5-dihydro-2-phenylfuran-3-carboxylate (4): A solution of zinc chloride in diethyl ether (0.60 mL, 1.00 M) was added to tetrahydrofuran (1 mL) followed by a solution of phenyl magnesium bromide in diethyl ether (0.19 mL, 3.20 M). Caution should be taken during this addition as these transmetallation reactions are exothermic. The solution was stirred for 1 h until a white precipitate was observed. Ethyl (±)-(2*RS*, 3*SR*)-tetrahydro-2-phenyl-3-(phenylsulfonyl)-4-methylenefuran-3-carboxylate **(3)** (0.05 mg, 0.13 mmol) and Pd(PPh$_3$)$_4$ (16 mg, 13 μmol) were added and the reaction stirred under nitrogen for 18 h. The reaction was quenched with saturated aqueous ammonium chloride solution (2 mL) and then divided between water (10 mL) and ethyl acetate (20 mL). The organic phase was dried (Na_2SO_4) and the solvents removed in vacuo. The residue was purified by column chromatography over silica gel eluting with 20% diethyl ether in petroleum ether. The title compound was obtained as a colourless oil (26 mg, 63%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 5.1 min. – IR: $\tilde{\nu}_{max}$ = 3058 cm^{-1}, 3024, 2980, 2892, 2835, 1712 (CO), 1660 (CO), 1494, 1452, 1372, 1313, 1256, 1111, 1039, 942, 836, 757, 699. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35 (m, 5 H, Ph), 6.03 (dd, ^4J = 6 ^4J = 3 Hz, 1 H, H-2), 4.87 (dd, ^2J = 15 ^4J = 6 Hz, 1 H, H-5$_a$), 4.87 (dd, ^2J = 15 ^4J = 3 Hz, 1 H, H-5$_b$), 4.14 (m, 4 H, ArCH_2 OCH_2CH$_3$), 1.15 (t, 3 H, OCH$_2$CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 (OCH$_2$*C*H$_3$), 33.3 (Ar*C*H$_2$), 60.8 (O*C*H$_2$CH$_3$), 78.5 (C-5), 89.6 (C-2), 127.4 (ArC), 128.0 (ArC), 128.4 (ArC), 128.6 (ArC), 128.8 (ArC), 129.2 (ArC), 129.3 (ArC), 138.2 (ArC), 142.1 (C-4), 153.1 (C-3), 163.7 (CO). – EI-MS: *m*/*z* = 308 (6) [M$^+$], 105 (40) [PhCO$^+$], 91 (100) [PhCH$_2^+$], 77 (24) [Ph$^+$].

Ethyl (±)-2,5-Dihydro-2-phenyl-4-(*o*-trifluoromethyl)benzylfuran-3-carboxylate (5): The title compound was obtained as a colourless oil (81%). R_f = 0.7 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 4.8 min. – IR: $\tilde{\nu}_{max}$ = 3066 cm^{-1}, 3034, 2978, 2851, 1715 (CO), 1665 (CO), 1610, 1587, 1495, 1456, 1373, 1317, 1258, 1176, 1152, 1114, 1061, 1040, 945, 839, 800, 770, 758, 702. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69 (d, ^3J = 7 Hz, 1 H, ArH-6), 7.45 (m, 3 H, ArH), 7.32 (m, 5 H, Ph), 6.00 (dd, ^4J = 3 ^4J = 6 Hz, 1 H, H-2), 4.73 (dd, ^2J = 15 ^4J = 6 Hz, 1 H, H-5$_a$), 4.60 (dd, ^2J = 15 ^4J = 3 Hz, 1 H, H-5$_b$), 4.35 (d, ^2J = 16 Hz, 1 H, ArCH), 4.29 (d, ^2J = 16 Hz, 1 H, ArCH), 4.15 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 4.0 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 1.12 (t, ^3J = 7 Hz, 3 H, CH$_2$CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 (OCH$_2$*C*H$_3$), 29.8 (Ar*C*H$_2$), 61.0 (O*C*H$_2$CH$_3$), 78.4 (C-5), 89.6 (C-2), 125.1 (q, $^2J_{F–C}$ = 273 Hz, CF_3), 126.8 (q, $^3J_{F–C}$ = 6 Hz, ArC-1′), 127.7 (s, ArC-4′), 128.0 (ArC-2), 128.8 (ArC-4), 129.0 (ArC-3), 129.3 (ArC-1), 129.7 (s, ArC-3′), 131.5 (s, ArC-5′), 132.8 (q, $^4J_{F–C}$ = 1 Hz, ArC-6′), 136.7 (q, $^4J_{F–C}$ = 2 Hz, ArC-2′), 142.0 (C-

4), 151.9 (C-3), 163.7 (CO). – ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –60.08 (s, CF_3). – EI-MS: *m*/*z* = 376 (4) [M^+], 303 (50) [M – $CO_2Et]^+$, 217 (56) [M – $CF_3PhCH_2]^+$, 159 (100) [$CF_3PhCH_2]^+$, 105 (60) [$PhCO^+$], 77 (22) [Ph^+].

Ethyl (±)-2,5-Dihydro-4-(*p*-*N*,*N*-dimethylamino)benzyl-2-phenylfuran-3-carboxylate (6): The title compound was obtained as a colourless oil (61%). R_f = 0.4 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 8.2 min. – IR: $\tilde{\nu}_{max}$ = 3062 cm^{-1}, 3031, 2960, 2907, 2842, 1714 (CO), 1660 (CO), 1613, 1518, 1454, 1369, 1352, 1257, 1158, 1110, 1038, 947, 910, 807, 700. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (m, 5 H, Ph), 7.15 (d, ^3J = 8 Hz, 2 H, ArH-3), 6.72 (d, ^3J = 8 Hz, 2 H, ArH-2), 5.97 (dd, ^4J = 6, ^4J = 3 Hz, 1 H, H-2), 4.85 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5_a), 4.70 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5_b), 4.16 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 4.09 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 4.03 (d, ^2J = 15 Hz, 1 H, ArC*H*), 3.90 (d, ^2J = 15 Hz, 1 H, ArC*H*), 2.96 (s, 6 H, NCH_3), 1.09 (t, ^3J = 7 Hz, 3 H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 (OCH_2CH_3), 32.4 (ArCH_2), 41.3 (NCH_3), 60.7 (OCH_2CH_3), 78.8 (C-5), 89.7 (C-2), 113.6 (ArC-2′), 126.0 (ArC-1′), 127.6 (ArC-1), 128.0 (ArC-2), 128.6 (ArC-4), 128.8 (ArC-3), 129 (ArC-3′), 142.4 (ArC-4′), 150.2 (C-4), 154.3 (C-3), 163.9 (CO). – EI-MS: *m*/*z* = 351 (56) [M^+], 172 (34) [M – Me_2NPh – $CO_2Et]^+$, 158 (22) [M – Me_2NPhCH_2 – $CO_2Et]^+$, 134 (100) [$Me_2NPhCH_2]^+$, 105 (63) [$PHCO^+$], 77 (43) [Ph^+].

Ethyl (±)-2,5-Dihydro-2-phenyl-4-(prop-3-ene)furan-3-carboxylate (7): The title compound was obtained as a colourless oil (72%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 3.1 min. – IR: $\tilde{\nu}_{max}$ = 3068 cm^{-1}, 3018, 6962, 2921, 2844, 1716 (CO), 1667 (CO), 1639, 1554, 1370, 1312, 1258, 1179, 1108, 1036, 917, 797, 754, 700. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.30 (m, 5 H, Ph), 5.95 (dd, ^4J = 5, ^4J = 4 Hz, 1 H, H-2), 5.87 (ddt, $^2J_{trans}$ = 17, $^2J_{cis}$ = 10, ^3J = 7 Hz, 1 H, H-2′), 5.19 (dd, $^2J_{trans}$ = 17, ^2J = 2 Hz, 1 H, H-3′), 5.13 (dd, $^2J_{cis}$ = 10, ^2J = 2 Hz, 1 H, H-3′), 4.95 (dd, ^2J = 15, ^4J = 5 Hz, 1 H, H-5_a), 4.79 (dd, ^2J = 15, ^4J = 4 Hz, 1 H, H-5_b), 4.08 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 4.05 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 3.48 (dd, ^2J = 15, ^3J = 7 Hz, 1 H, H-1′), 3.41 (dd, ^2J = 15, ^3J = 7 Hz, 1 H, H-1′), 1.11 (t, ^3J = 7 Hz, 3 H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6 (OCH_2CH_3), 31.7 (C-1′), 60.8 (OCH_2CH_3), 78.7 (C-5), 89.7 (C-2), 118.2 (C-2′), 127.9 (ArC-3), 128.3 (ArC-1), 128.7 (ArC-4), 128.9 (ArC-2), 134.0 (C-3′), 142.0 (C-4), 152.6 (C-3), 163.7 (CO). – EI-MS: *m*/*z* = 258 (8) [M^+], 217 (51) [M – $C_3H_5]^+$, 185 (57) [M – $CO_2Et]^+$, 144 (14) [M – CO_2Et – $C_3H_5]^+$, 105 (98) [$PhCO^+$], 77 (100) [Ph^+].

Ethyl (±)-2,5-Dihydro-2-phenyl-4-(2-phenylprop-3-ene)furan-3-carboxylate (8): The title compound was obtained as a colourless oil (85%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 6.0 min. – $C_{22}H_{22}O_3$ (334.3): calcd. C 79.0, H 6.6; found C 79.2, H 6.4. – IR: $\tilde{\nu}_{max}$ = 3084 cm^{-1}, 3057, 3014, 2980, 2932, 2899, 2843, 1712 (CO), 1664 (CO), 1627, 1604, 1493, 1453, 1446, 1368, 1308, 1254, 1165, 1116, 1041, 910, 782, 761, 700. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.04–7.52 (br. m, 10 H, ArH), 5.89 (dd, ^4J = 5, ^4J = 3 Hz, 1 H, H-2), 5.46 (d, ^2J = 1 Hz, 1 H, H-3′), 5.23 (d, ^2J = 1 Hz, 1 H, H-3′), 4.76 (dd, ^2J = 15, ^4J = 5 Hz, 1 H, H-5_a), 4.65 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5_b), 4.26 (d, ^2J = 16 Hz, 1 H, H-1′), 4.08 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 4.06 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 3.77 (d, ^2J = 16 Hz, 1 H, H-1′), 1.11 (t, ^3J = 7 Hz, 3 H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6 (OCH_2CH_3), 33.6 (C-1′), 60.8 (OCH_2CH_3), 78.7 (C-5), 89.7 (C-2), 115.3 (C-3′), 126.7 (ArC-3), 127.9 (ArC-4, ArC-3′), 128.6 (ArC-1, ArC-4′), 128.8 (ArC-2), 129.1 (ArC-2′), 140.4 (ArC-1′), 142.1 (C-4), 145.0 (C-2′), 152.7 (C-3), 163.7 (CO). – EI-MS: *m*/*z* = 334 (16) [M^+], 261 (37) [M – $CO_2Et]^+$, 231 (16) [M – $PhC_2H_2]^+$, 215 (70) [M – $PhC_3H_5]^+$, 105 (100) [$PHCO^+$], 77 (94) [Ph^+].

Ethyl (±)-2,5-Dihydro-2-phenyl-4-(phenylsulfonyl)methylenefuran-3-carboxylate (10): $Pd(PPh_3)_4$ (31 mg, 27 μmol) and ethyl (±)-(2*RS*,3*SR*)-tetrahydro-2-phenyl-3-(phenylsulfonyl)-4-methylenefuran-3-carboxylate **(3)** (0.05 mg, 0.13 mmol) were dissolved in tetrahydrofuran (1 mL) and the solution stirred for 18 h. The solvents were removed in vacuo and the residue purified by column chromatography over silica gel. Crystallisation from CH_2Cl_2 and ethanol afforded the title compound as a colourless solid (36 mg, 72%). m.p. 101–104°C. R_f = 0.1 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 8.6 min. – IR: $\tilde{\nu}_{max}$ = 3042 cm^{-1}, 2917, 2844, 1717 (CO), 1665 (CO), 1562, 1481, 1434, 1324 (SO_2), 1261, 1160 (SO_2), 1126, 1097, 1028, 912, 734, 697. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.94 (d, ^3J = 6 Hz, 2 H, ArH-2′), 7.66 (t, *J* = 6 Hz, 1 H, ArH-4′), 7.52 (t, *J* = 6 Hz, 2 H, ArH-3′), 7.32 (m, 5 H, Ph), 5.87 (dd, ^4J = 3, ^4J = 6 Hz, 1 H, H-2), 5.20 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5_a), 5.03 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5_b), 4.70 (d, ^2J = 14 Hz, 1 H, H-1′), 4.08 (d, ^2J = 14 Hz, 1 H, H-1′), 3.82 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 3.77 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 10.97 (t, ^3J = 7 Hz, 3 H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4 (OCH_2CH_3), 54.6 (C-5), 61.3 (OCH_2CH_3), 78.3 (PhO_2SCH_2), 89.1 (C-2), 127.3 (ArC-3′), 128.0 (ArC-3), 128.2 (ArC-4′), 128.3 (ArC-4), 128.4 (ArC-2′), 129.1 (ArC-2), 129.7 (ArC-1), 130.5 (ArC-1′), 134.0 (C-4), 139.7 (C-3), 163.6 (CO). – EI-MS: *m*/*z* = 231 (28) [M – $SO_2Ph]^+$, 185 (64) [M – SO_2Ph – $OEt]^+$, 157 (36) [M – SO_2Ph – $CO_2Et]^+$, 105 (22) [$PhCO^+$], 77 (100) [Ph^+].

Ethyl (±)-2,5-Dihydro-4-methyl-2-phenylfuran-3-carboxylate (13): The title compound was synthesised according to the general procedure employed for the synthesis of benzyl and allyl-substituted 2,5-dihydrofurans, but using benzyl magnesium chloride in diethyl ether (0.60 mL, 1.00 M) instead of phenyl magnesium chloride. The title compound was obtained as a colourless oil (21 mg, 68%). R_f = 0.5 (20% EtOAc in petroleum ether, SiO_2). – GC: R_t = 2.8 min. – IR: $\tilde{\nu}_{max}$ = 3062 cm^{-1}, 3030, 2983, 2924, 2845, 1712 (CO), 1669 (CO), 1492, 1457, 1380, 1324, 1254, 1117, 1095, 1045, 945, 838, 757, 700. – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31 (m, 5 H, Ph), 5.95 (dd, ^4J = 4, ^4J = 3 Hz, 1 H, H-2), 4.96 (dd, ^2J = 14, ^4J = 4 Hz, 1 H, H-5_a), 4.81 (dd,, ^2J = 14, ^4J = 3 Hz 1 H, H-5_b), 4.09 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 4.07 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OC$H_2$$CH_3$), 2.20 (s, 3 H, CH_3), 1.13 (t, ^3J = 7 Hz, 3 H, CH_2CH_3). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.9 (CH_3), 14.5 (OCH_2CH_3), 60.0 (OCH_2CH_3), 78.4 (C-5), 89.6 (C-2), 128.0 (ArC-3), 128.8 (ArC-4), 129.0 (ArC-2), 129.3 (ArC-1), 142.0 (C-4), 151.9 (C-3), 163.7 (CO). – EI-MS: *m*/*z* = 232 (22) [M^+], 217 (8) [M – $CH_3]^+$, 186 (31) [M – $OEt]^+$, 159 (100) [M – $CO_2Et]^+$, 105 (61) [$PhCO^+$], 77 (69) [Ph^+].

Method for the Synthesis of Ethyl 4-Alkyl-2,5-dihydro-2-phenylfuran-3-carboxylate: Ethyl (±)-2,5-Dihydro-2-phenyl-4-propylfuran-3-carboxylate (15): The title compound was synthesised according to the general procedure employed for the synthesis of benzyl and allyl-substituted 2,5-dihydrofurans, but using ethyl magnesium bromide in diethyl ether (0.20 mL, 1.90 M) instead of phenyl magnesium chloride and omitting the $Pd(PPh_3)_4$ catalyst. The title compound was obtained as a colourless oil (30 mg, 86%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO_2). GC: R_t = 3.2 min. – IR: $\tilde{\nu}_{max}$ = 3029 cm^{-1}, 2960, 2921, 2863, 1712 (CO), 1659 (CO), 1554, 1374, 1258, 1100, 1047, 1024, 908, 798, 733, 698. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31 (m, 5 H, Ph), 5.94 (dd, ^4J = 6, ^4J = 3 Hz, 1 H, H-2), 4.96 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5_a), 4.79 (dd, ^2J = 15,

^4J = 3 Hz, 1 H, H-5$_b$), 4.04 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 3.98 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 2.66 (m, 2 H, H-1′), 1.62 (hept., ^3J = 7 Hz, 2 H, H-2′), 1.10 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 1.02 (t, ^3J = 7 Hz, 3 H, H-3′). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.6 (C-1′), 14.8 (OCH$_2$*C*H$_3$), 22.2 (C-2′), 29.0 (C-3′), 60.6 (O*C*H$_2$CH$_3$), 78.9 (C-5), 89.6 (C-2), 128.0 (ArC-2), 128.1 (ArC-1), 128.7 (ArC-4), 128.8 (ArC-3), 142.4 (C-4), 155.5 (C-3), 163.9 (CO). – EI-MS: *m*/*z* = 260 (8) [M$^+$], 217 (97) [M – C$_3$H$_7$]$^+$, 187 (100) [M – CO$_2$Et]$^+$, 158 (62) [M – CO$_2$Et – C$_2$H$_5$]$^+$, 145 (19) [M – CO$_2$Et – C$_3$H$_7$]$^+$, 105 (100) [PHCO$^+$], 77 (69) [Ph$^+$].

Ethyl (±)-4-*iso*-Butyl-2,5-dihydro-2-phenylfuran-3-carboxylate (16): The title compound was obtained as a colourless oil (61%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO$_2$). – GC: R_t = 3.3 min. – C$_{17}$H$_{22}$O$_3$ (274.3): calcd. C 74.4, H 8.1; found C 74.1, H 8.3. – IR: $\tilde{\nu}_{max}$ = 3061 cm^{-1}, 3028, 2959, 2935, 2868, 1715 (CO), 1660 (CO), 1456, 1370, 1318, 1252, 1204, 1108, 1050, 944, 847, 756, 700. – ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.34 (m, 5 H, ArH), 5.93 (t, ^4J = 6, ^4J = 3 Hz, 1 H, H-2), 4.95 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5$_a$), 4.77 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5$_a$), 4.06 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 4.00 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 2.64 (dd, ^2J = 13, ^3J = 8 Hz, 1 H, CHCH_2), 2.52 (dd, ^2J = 13, ^3J = 7 Hz, 1 H, CHCH_2), 1.88 (m, 1 H, C*H*CH$_2$), 1.10 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 1.01 (d, ^3J = 6 Hz, 3 H, CHCH_3), 0.99 (d, ^3J = 6 Hz, 3 H, CHCH_3). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.6 (OCH$_2$*C*H$_3$), 23.3 (CH*C*H$_3$), 23.4 (CH*C*H$_3$), 28.7 (CH*C*H$_2$), 36.0 (*C*HCH$_2$), 60.6 (O*C*H$_2$CH$_3$), 79.4 (C-5), 89.7 (C-2), 128.0 (ArC-3), 128.6 (ArC-4), 128.7 (ArC-2), 128.9 (ArC-1), 142.4 (C-4), 154.6 (C-3), 163.9 (CO). – EI-MS: *m*/*z* = 274 (5) [M$^+$], 217 (57) [M – C$_4$H$_9$]$^+$, 201 (82) [M – CO$_2$Et]$^+$, 158 (52) [M – C$_3$H$_7$ – CO$_2$Et]$^+$, 105 (100) [M – C$_4$H$_9$]$^+$, 77 (56) [Ph$^+$].

Ethyl (±)-2,5-Dihydro-4-(methylenecyclohexyl)-2-phenylfuran-3-carboxylate (17): The title compound was obtained as a colourless oil (71%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO$_2$). – GC: R_t = 5.0 min. – IR: $\tilde{\nu}_{max}$ = 3028 cm^{-1}, 2930, 2848, 1712 (CO), 1657 (CO), 1449, 1371, 1250, 1183, 1115, 1046, 944, 837, 755, 698. – ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.32 (m, 5 H, Ph), 5.94 (dd, ^4J = 6, ^4J = 3 Hz, 1 H, H-2), 4.93 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5$_a$), 4.76 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5$_b$), 4.04 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 4.00 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 2.62 (dd, ^2J = 13, ^3J = 7 Hz, 1 H, CHCH_2), 2.53 (dd, ^2J = 13, ^3J = 6 Hz, 1 H, CHCH_2), 1.73 (m br, 6 H, CH$_2$), 1.26 (m, 5 H br, CH, CH$_2$), 1.10 (t, ^4J = 7 Hz, 3 H, OCH$_2$CH_3). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.6 (OCH$_2$*C*H$_3$), 26.8 (CH$_2$), 27.0 (CH$_2$), 34.1 (CH$_2$), 34.6 (*C*HCH$_2$), 38.0 (CH*C*H$_2$), 60.6 (O*C*H$_2$CH$_3$), 79.5 (C-5), 89.6 (C-2), 128.0 (ArC-2), 128.1 (ArC-1), 128.6 (ArC-4), 128.9 (ArC-3), 142.4 (C-4), 154.5 (C-3), 164.0 (CO). – EI-MS: *m*/*z* = 241 (29) [M – CO$_2$Et]$^+$, 217 (15) [M – C$_7$H$_{13}$]$^+$, 158 (55) [M – C$_6$H$_{11}$ – CO$_2$Et]$^+$, 105 (100) [PhCO$^+$], 77 (60) [Ph$^+$].

Ethyl (±)-4-(5-Chloropentyl)-2,5-dihydro-2-phenylfuran-3-carboxylate (18): The title compound was obtained as a colourless oil (42%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO$_2$). – GC: R_t = 5.9 min. – IR: $\tilde{\nu}_{max}$ = 3060 cm^{-1}, 3029, 2955, 2922, 2848, 1713 (CO), 1657 (CO), 1493, 1454, 1373, 1308, 1259, 1111, 1091, 1047, 1022, 907, 835, 798, 756, 700. – ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.32 (m, 5 H, ArH), 5.93 (dd,, ^4J = 6, ^4J = 4 Hz 1 H, H-2), 4.96 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5$_a$), 4.88 (dd, ^2J = 15, ^4J = 4 Hz, 1 H, H-5$_b$), 4.03 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 4.01 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 3.56 (t, ^3J = 7 Hz, 2 H, CH$_2$Cl), 2.73, (m, 2 H, H-1′), 1.84 (m, 2 H, H-4′), 1.26 (m, 2 H, H-2′), 1.10 (t, ^3J = 7 Hz, 3 H, OCH$_2$CH_3), 0.87 (m, 2 H, H-3′). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.6 (OCH$_2$*C*H$_3$), 26.9 (C-3′), 27.5 (C-2′), 28.1 (C-4′), 32.9 (C-1′), 45.5 (C-5′), 60.7 (O*C*H$_2$CH$_3$), 78.9 (C-5), 89.7 (C-2), 127.9 (ArC-2), 128.1 (ArC-4), 128.7 (ArC-1), 128.9 (ArC-3), 142.3 (C-4), 155.1 (C-3), 163.8 (CO). – EI-MS: *m*/*z* = 322 (2) [M$^+$], 249 (80) [M – CO$_2$Et]$^+$, 217 (100) [M – CO$_2$Et – C$_5$H$_{10}$Cl]$^+$), 158 (27) [M – CO$_2$Et – C$_4$H$_8$Cl]$^+$, 145 (10) [M – CO$_2$Et – C$_5$H$_{10}$Cl]$^+$, 105 (73) [PhCO$^+$], 77 (23) [Ph$^+$] all peaks exhibited the appropriate isotope pattern.

Ethyl (±)-2,5-Dihydro-2-phenyl-4-(3-phenylpropyl)furan-3-carboxylate (19): The title compound was obtained as a colourless oil (35%). R_f = 0.6 (20% EtOAc in petroleum ether, SiO$_2$). – GC: R_t = 6.5 min. – IR: $\tilde{\nu}_{max}$ = 3080 cm^{-1}, 3059, 3026, 2978, 2913, 2850, 1718 (CO), 1660 (CO), 1605, 1492, 1453, 1361, 1251, 1088, 1044, 1026, 752, 699. – ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.33–7.19 (m, 10 H, ArH), 5.93 (dd, ^4J = 6, ^4J = 3 Hz, 1 H, H-2), 5.57 (dd, ^2J = 15, ^4J = 6 Hz, 1 H, H-5$_a$), 4.79 (dd, ^2J = 15, ^4J = 3 Hz, 1 H, H-5$_b$), 4.03 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 4.01 (dq, ^2J = 11, ^3J = 7 Hz, 1 H, OCH_2CH$_3$), 2.72 (m, 4 H, CH_2CH$_2$CH_2), 1.88 (pent., ^3J = 7 Hz, 2 H, CH$_2$CH_2CH$_2$), 1.08 (t ^3J = 7 Hz, 3 H,, OCH$_2$CH_3). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.6 (OCH$_2$*C*H$_3$), 27.0 (C-2′), 30.6 (C-1′), 30.7 (C-3′), 60.7 (O*C*H$_2$CH$_3$), 78.9 (C-5), 89.7 (C-2), 126.7 (ArC), 127.9 (ArC), 128.8 (ArC), 128.7 (ArC), 128.9 (ArC), 129.01 (ArC), 129.1 (ArC), 129.4 (ArC), 142.3 (C-4), 155.0 (C-3), 163.8 (CO). – EI-MS: *m*/*z* = 336 (2) [M$^+$], 263 (5) [M – CO$_2$Et]$^+$, 217 (23) [M – PhC$_3$H$_6$]$^+$,158 (17) [M – CO$_2$Et – PhC$_2$H$_4$]$^+$, 143 (6) [M – CO$_2$Et – PhC$_3$H$_6$]$^+$, 105 (57) [PhCO$^+$], 91 (100) [PhCH$_2^+$], 77 (38) [Ph$^+$].

Acknowledgments

The authors wish to thank the European Union TMR programme for a Fellowship (MW) and Prof. A. Alexakis, University of Geneva, for useful discussion.

[1] For a recent review see: S. Kobayashi, *Chem. Soc. Rev.* **1999**, *28*, 1–16.
[2] [2a] X. Marat, N. Monteiro, G. Balme, *Synlett* **1997**, 845–847. – [2b] B. Clique, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1301–1304.
[3] M. Cavicchioli, E. Sixdenier, A. Derrey, D. Bouyssi, G. Balme, *Tetrahedron Lett.* **1997**, *38*, 1763–1766.
[4] N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**; B. M. Trost; *Bull. Chem. Soc. Jpn*. **1988**, *61*, 107–124.
[5] For reviews of organozinc chemistry see: [5a] E. Erdik, *Tetrahedron* **1992**, *48*, 9577–9648. – [5b] P. Knochel, in *Transition Metals for Organic Synthesis* (Eds.: M. Beller and C. Bolm), Wiley-VCH, Weinheim, **1998**, Vol 1, p. 467. – [5c] P. Knochel, in *Metal-catalysed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 387.
[6] For a comprehensive discussion of organocuprates the reader is referred to: R. J. K. Taylor, *Organocopper Reagents: A Practical Approach*, OUP, Oxford, **1994**.
[7] [7a] A. Orita, A. Watanabe, H. Tsuchiya, J. Otera, *Tetrahedron* **1999**, *55*, 2889–2898. – [7b] H. Matsushita, E.-I. Negishi, *J. Chem. Soc., Chem. Commun.* **1982**, 160–161; J.-C. Fiaud, L. Ariki-Zouioueche, *J. Organomet. Chem.* **1985**, *295*, 383–388.
[8] C. Gosmini, J. Y. Nédélec, J. Périchon, *Tetrahedron Lett.* **1997**, *38*, 1941–1942.
[9] M. V. Hanson, J. D. Brown, R. D. Rieke, Q. J. Niu, *Tetrahedron Lett.* **1994**, *35*, 7205–7208; R. D. Rieke, M. V. Hanson, J. D. Brown, Q. J. Niu, *J. Org. Chem.* **1996**, *61*, 2726–2730; A. Guijarro, D. M. Rosenberg, R. D. Rieke, *J. Am. Chem. Soc.* **1999**, *121*, 4155–4167.
[10] D. Villemin, A. B. Alloum, *Synth. Commun.* **1991**, *21*, 63–68; G. R. Reddy, S. V. S. A. K. Gupta, D. B. Reddy, B. Seenaiah, *J. Indian Chem. Soc.* **1992**, *69*, 396–397.
[11] F. Cariati, L. Naldini, *Gazz. Chim. Ital.* **1965**, 3–15.
[12] T. Tsuda, Y. Horii, Y. Nakagawa, T. Ishida, T. Saegusa, *J. Org. Chem.* **1989**, *54*, 977–979.

[13] H. Matsushita, E.-I Negishi, *J. Am. Chem. Soc.* **1981**, *103*, 2882–2884; T. Hayashi, A. Yamamoto, T. Hagihara, *J. Org. Chem.* **1986**, *51*, 723–727; H. Matsushita, S. Chatterjee, E.-I. Negishi, *Tetrahedron Lett.* **1981**, *22*, 3737–3740.

[14] E.-I. Negishi, Y. Noda, F. Lamaty, E. J. Vauter, *Tetrahedron Lett.* **1990**, *31*, 4393–4396; M. Rottländer, P. Knochel, *Tetrahedron Lett.* **1997**, *38*, 1749–1752; Y. Nakamura, M. Matsumoto, Y. Hayashida, J. Nishimura, *Tetrahedron Lett.* **1997**, *38*, 1983–1986.

[15] M. Julia, M. Nel, D. Uguen, *Bull. Soc. Chim. Fr.* **1987**, 487–492; The importance of the magnesium salts in this reaction is also supported by the observation that when the allylic sulfone **3** is treated with diethyl zinc only traces of the substituted 2,5-dihydrofuran are obtained.

[16] J. Tsuji, *Palladium Reagents and Catalysts; Innovations in Organic Synthesis*, Wiley, Chichester, **1995** and references cited therein.

[17] [17a] C. Copéret, T. Sugihara, G. Wu, I. Shimoyama, E-I. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 3422–3431. – [17b] G. K. Friestad, B. P. Branchaud, *Tetrahedron Lett.* **1995**, *36*, 7047–7050.

[18] H. Matsushita, E-I Negishi, *J. Org. Chem.* **1982**, *47*, 4161–4165.

[19] E. Keinan, Z. Roth, *J. Org. Chem.* **1983**, *48*, 1769–1772; E. Keinan, M. Peretz, *J. Org. Chem*. **1983**, *48*, 5302–5309; S. Torii, H. Tanaka, T. Katch, K. Morisaki, *Tetrahedron Lett.* **1984**, *25*, 3207–3208.

[20] All attempts to incorporate other electrophiles proved unsuccessful with the starting sulfone **3** recovered in quantitative yield.

[21] S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967**, *9*, 165–168. For an excellent protocol the reader is referred to p. 54 of ref.[5]

Received November 9, 1999
[O99627]