Synthesis of [^{2}H,^{13}C]-Labelled Diallylmalonates − Useful Probes for the Study of Transition Metal-Catalysed 1,6-Diene Cycloisomerisation

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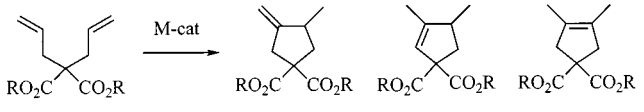
Reliable synthetic routes to isotopically labelled dimethyl [^{13}C,^{2}H]diallylmalonates (**1**) have been developed. Dimethyl diallylmalonates readily undergo transition-metal catalysed cycloisomerisation and the isotopically labelled substrates are expected to be of general utility in the study of the mechanism of such reactions. In the synthetic routes developed, the ^{2}H labelled allyl chains were introduced by reduction of propargyl functionality with Schwartz reagent. The regio- and stereo-selectivity of such reactions allowing highly selective labelling strategies. The ^{13}C labelled allyl chains were introduced via Pd-catalysed allylic alkylation of ^{13}C- or ^{2}H-labelled dimethyl allylmalonate anions using [3-$^{13}C_1$]allyl benzoate as the allylic electrophile. Using these methods, dimethyl [1,7-(*E,E*)-$^2H_2$]hept-1,6-dienyl-4,4-dicarboxylate (**5**), dimethyl [2,6-$^2H_2$]hept-1,6-dienyl-4,4-dicarboxylate (**6**), dimethyl [1,7-(*Z,Z*)-$^2H_2$]hept-1,6-dienyl-4,4-dicarboxylate (**7**), dimethyl [1,1,2,6,7,7-$^2H_6$]hept-1,6-dienyl-4,4-dicarboxylate (**8**), dimethyl [1,3-$^{13}C_1$,5,7-$^{13}C_1$]hept-1,6-dienyl-4,4-dicarboxylate (**9**), dimethyl [1,3-$^{13}C_1$,6-$^2H_1$]hept-1,6-dienyl-4,4-dicarboxylate (**10**), and dimethyl [1,3-$^{13}C_1$,7-(*E*)-$^2H_1$]hept-1,6-dienyl-4,4-dicarboxylate (**11**) have been prepared.

Introduction

Cycloisomerisation reactions of dienes, enynes, and diynes represent a powerful method for the synthesis of carbocyclic and heterocyclic rings with regio- and stereocontrol.[1] The first report of the transition metal catalysed (Rh) cycloisomerisation of 1,6-dienes was by Shaw et al. in 1971.[2] Since then a number of other transition metal[3−8] and lanthanide[9] complexes have also been reported for this reaction. Of note is the reliable chemistry of malonates which has made dialkyl hept-1,6-dienyl-4,4-dicarboxylates **1** (i.e. diallylmalonates) popular substrates for the study and development of 1,6-diene cycloisomerisation reactions[3,5,6,7] (Scheme 1, R is usually Me or Et).



Scheme 1. Cycloisomerisation of the 1,6-diene **1** (R = Me, Et etc.) to cyclopentenes **2**, **3**, and **4**

Important features in the cycloisomerisation of **1** are control of regioselectivity (**2** versus **3** versus **4**) and stereochemistry (in **2** and **3**). Consequently, the discovery of novel catalytic systems[5,6,7] and design of ligands that induce enantioselectivity[7] have attracted much recent interest. For example, Itoh et al.,[5] have reported a range of Ru-based catalysts which are highly effective for cycloisomerisation with excellent regiocontrol. Thus, by use of [Ru(COD)Cl]$_n$ as pro-catalyst, **1** (R = Me) is cycloisomerised in *i*PrOH at 90 °C to give exclusively the *exo*-methylene isomer **2** in excellent (94%) yield. Radetich and RajanBabu[6] have developed the use of cationic complexes '[(L)M(allyl)][OTf]' (L = triarylphosphane, M = Pd or Ni) as effective pro-catalysts for cycloisomerisation. When M = Ni, **2** (R = Me) is obtained in 92% yield and when M = Pd, a mixture of **2** (22%) and **4** (78%) are obtained in overall 91% yield. Heumann and Moukhliss[7] have demonstrated the potential of enantiomerically pure *N,N*-ligands for Pd-catalysed cycloisomerisation by achieving promising enantioselectivity in conversion of **1** (R = Et) to **3** (up to 60% *ee*).

A knowledge of the mechanism(s) involved in cycloisomerisation would obviously be essential in understanding the selectivities induced by the various catalysts outlined above as well as being useful in the development of new catalysts. However, as far as we are aware, to date, only the preliminary studies of Grigg et al.,[3] have been reported. Nonetheless, for conversion of **1** into **2** it is obvious that at least one hydride migration is involved and that conversion (direct or indirect) of **1** into **3** or **4** involves at least two. To gain information about the mechanism it is therefore imperative that the hydride migration(s) be tracked between substrate and product. ^{2}H-labelling is an efficient method by which this may be achieved and thus by consideration of the three basic mechanisms that have been proposed[3,5,6] we devised a series of ^{2}H-labelling patterns for **1** (R = Me). Furthermore, since the symmetry of **1** can potentially pose problems in determining from where and to where the hydride has migrated, we also designed a number of ^{13}C-labelling strategies. Since cycloisomerisation of **1** to **2**, **3**, or **4** involves only H-migrations, ^{13}C-labelling allows distinction of one allyl chain (in **1** and products) from the other and also allows the origin and destination of *intermolecular* hydride migrations to be deduced. Our initial strategies for the synthesis of such ^{13}C-labelled substrates were based on 'routine' malonate chemistry leading to an aldehyde.[10] We

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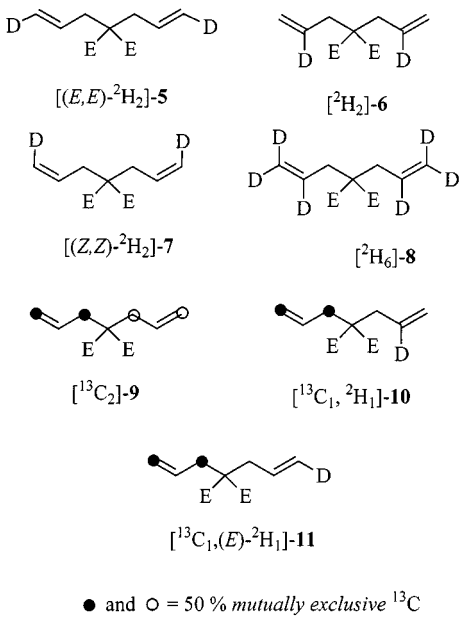
had some difficulties in finding conditions for this sequence and furthermore, the aldehyde unexpectedly failed to undergo the Wittig chemistry planned for installation of the ^{13}C label. Consequently we began to explore alternative strategies. Herein we describe these studies and report in full the synthesis and characterisation of symmetrically labelled [(*E*,*E*)-$^2H_2$]-**5**, [$^2H_2$]-**6**, [(*Z*,*Z*)-$^2H_2$]-**7**, [$^2H_6$]-**8**, and [$^{13}C_2$]-**9** and isotopically desymmetrised[11] doubly labelled substrates [$^{13}C_1$,$^2H_1$]-**10** and [$^{13}C_1$-(*E*)-$^2H_1$]-**11**.

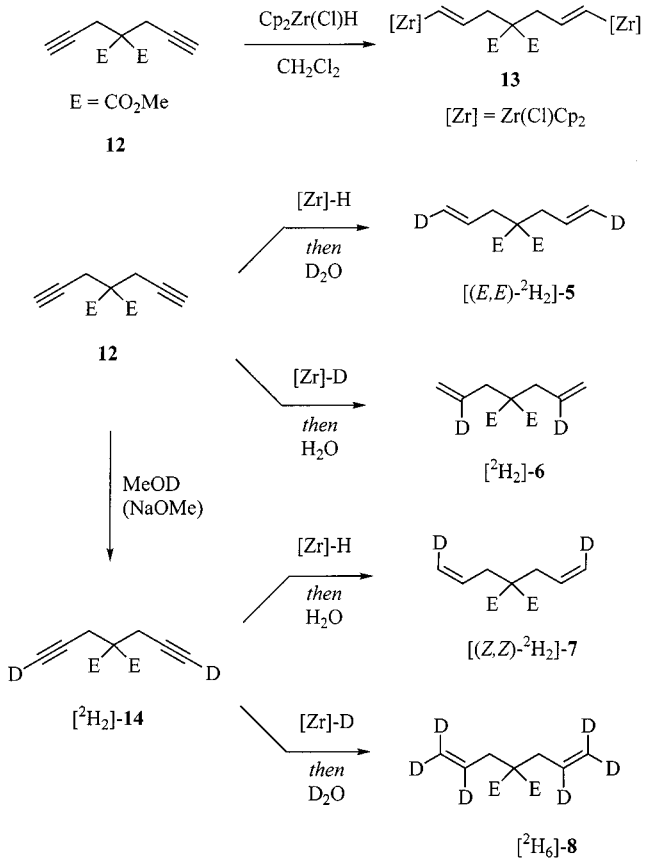


These labelled probes, used individually and in concert, have now proved of utility in the study of the mechanism of the Pd-catalysed conversion of **1** to **2**, **3**, and **4**[12] and we expect that they will prove of use in other systems.

Results and Discussion

Synthesis of Symmetrical ^2H-Labelled Substrates

Our strategy for the incorporation of ^2H-labels in the allyl groups of **1**,[13] lay in the regio- and stereo-selective reduction of propargylic to allylic functionality. Hydrozirconation of dimethyl dipropargyl malonate (**12**) using Schwartz reagent, followed by protolysis of the terminal allylic C−Zr bond (with H_2O) gave **1** without competing over-reduction of the intermediate alkenyl-zirconocene (**13**) or reduction of the ester functionality.[14] However, we found that with stoichiometric reagent, conversion was incomplete. We initially suspected that the malonate unit was acting as an efficient Zr-chelator and thereby sequestering reagent. To combat this we added Cp_2ZrCl_2 (1 equivalent) first and then the Schwartz reagent. However, this had no effect and the incomplete reduction traced to the quality of the commercial reagent.[15] Reactions were therefore performed by titration with Schwartz reagent until no substrate could be detected by TLC. Although reagent quality varied from batch to batch, typically we required ca. 1.2−1.5 equivalents of reagent per alkyne to be reduced. By using this method and then quenching intermediate **13** with D_2O (99.9% D) we obtained [(*E*,*E*)-$^2H_2$]-**5** in 80% yield, Scheme 2.



Scheme 2. The synthetic routes employed to generate ^2H-labelled dimethyl hept-1,6-dienyl-4,4-dicarboxylates **5**, **6**, **7**, and **8**

Careful ^1H, ^2H, and ^{13}C NMR analysis indicated that the deuterium location was exclusively at the double bond termini [C(1,7)] and with an (*E*)-geometry − thereby confirming that we had attained the high levels of regioselectivity and stereoselectivity required. However, the level of deuterium incorporation was not perfect (> 96% D_2). This was ascribed to the extreme sensitivity of the intermediate **13** towards adventitious water (i.e. unlabelled). The near-perfect regioselectivity obtained through hydrozirconation was exploited in the synthesis of the internally deuterated alkene isomer [$^2H_2$]-**6** (> 99% D_2) by use of deuterated Schwartz reagent, $Cp_2Zr(Cl)D$.

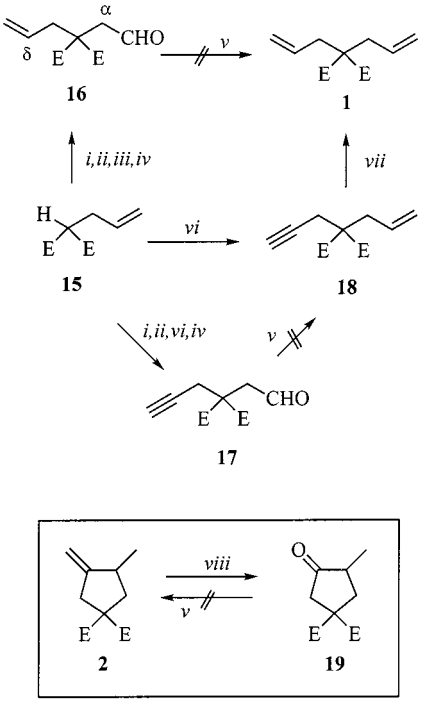
By deuterium−proton exchange of **12** with MeOD (cat. NaOMe) we obtained [$^2H_2$]-**14** which on hydrozirconation, then quenching with H_2O, gave [(*Z*,*Z*)-$^2H_2$]-**7** with very high deuterium incorporation (> 99% D_2). The room-temperature ^1H NMR 400 MHz spectrum of [*Z*,*Z*-$^2H_2$]-**7** in $CDCl_3$ is complicated by molecular tumbling at the ^2H-resonance frequency causing the three spin states to interchange at a sufficient rate to interfere with the multiplicity of the $^3J_{DH}$ (ca. 2.6 Hz, *trans*) scalar coupling. Consequently the internal C*H*=C signal becomes rather complex and not a double, triple (1,2,1) triplet (1,1,1) as ex-

pected. Switching to a lower field (270 MHz), or increased temperature (55 °C) or more viscous solvent (C_6D_6) had only marginal effects. The very high $^2H_2$ incorporation is supported by the absence of a singlet adjacent to the upfield shifted CHD [1:1:1] triplet at δ = 119.0 [C(1,7)] in the ^{13}C NMR spectrum.

The combination of deuterated alkyne [$^2H_2$]-**14** with deuterated Schwartz reagent facilitated synthesis of the all-deuterated alkene isomer [$^2H_6$]-**8** (> 96% D_6) by employing a D_2O quench. As with [(*E,E*)-$^2H_2$]-**5**, the slightly lower deuterium incorporation in [$^2H_6$]-**8** arises through adventitious water effecting nondeuterated protolysis of the alkenyl-zirconocene intermediates.

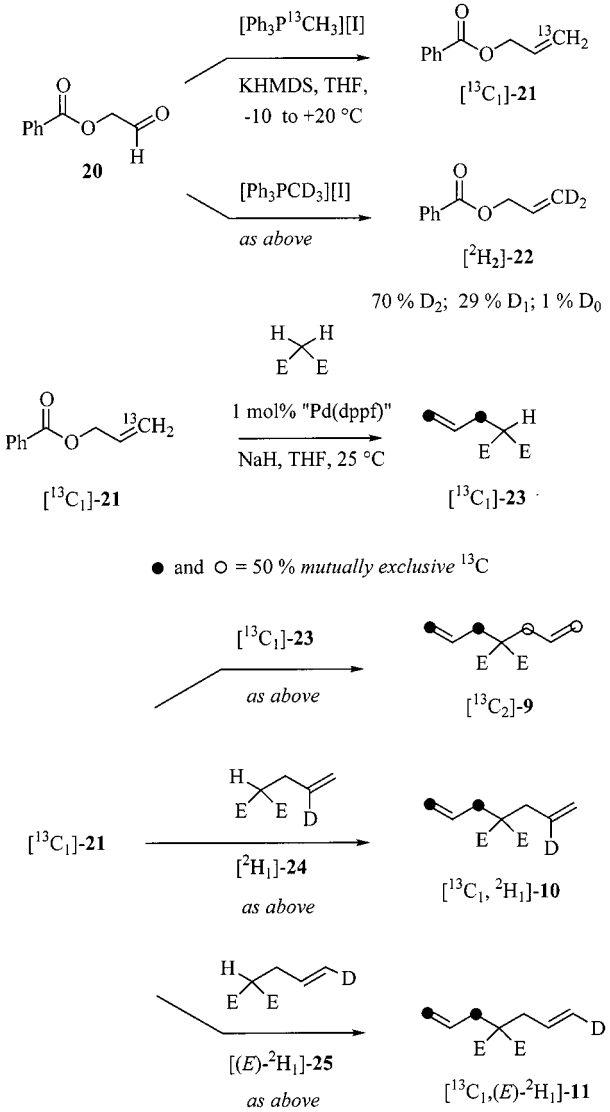
Synthesis of ^{13}C-Labelled Substrates

Our first strategy for the introduction of a single ^{13}C-label at the terminus of one of the allyl chains in **1** was based on introduction of the label at the last step of the synthesis via methylenation of aldehyde **16** with a ^{13}C-labelled Wittig reagent. The δ-bromo analogue of **16** has been reported as a substrate for radical cyclisation by Malacria et al.[10a] Based on this communication, we ozonolysed dimethyl allylmalonate (**15**), protected the resultant aldehyde as a dimethyl acetal, allylated, and then deprotected[16,17] with aq. TFA[17c] to give **16** − Scheme 3. Analogous propargylation instead of allylation afforded **17** and propargylation of **15** afforded **18**. A test reaction confirmed that **18** could be selectively reduced to **1**.



Scheme 3. Routes attempted in the generation of ^{13}C-labelled dimethyl hept-1,6-dienyl-4,4-dicarboxylate (**1**). Conditions: *i*, O_3, MeOH (88%); *ii*, $(MeO)_3CH$, cat. $TsOH{\cdot}H_2O$ (79%); *iii*, allyl bromide, NaH, THF (50%); *iv*, TFA, CH_2Cl_2 (74%); *v*, range of Wittig-type methylenation conditions; *vi*, propargyl bromide, NaH, THF (75%); *vii*, $Cp_2Zr(Cl)$, CH_2Cl_2; *viii*, $NaIO_4$, CCl_4, MeCN, H_2O, cat. $RuCl_3{\cdot}H_20$ (79%)

However, to our dismay, all Wittig-type reagents that we could derive from MeI (our intended source of the ^{13}C label) completely failed to methylenate **16** (→ **1**) or **17** (→ **18**) under a range of conditions.[18] Attempted methylenation of ketone **19**,[19] generated from **2**[5] through oxidative cleavage under Sharpless conditions,[20] also failed. It thus appears that such reactions are incompatible with the malonate residue. Indeed, we could find no published examples of Wittig-type olefination of an aldehyde with malonate functionality at the β-position. We therefore turned our attention to methods by which we could attach a pre-^{13}C-labelled allyl chain to a malonate unit. A Pd-catalysed allylic alkylation reaction[21] employing a ^{13}C-labelled allylic electrophile[22] and a malonate anion seemed a reasonable method. Even though this would generate a 1:1 mixture of [1-$^{13}C_1$]- and [3-$^{13}C_1$]-labelling patterns which complicates the ^1H NMR spectra, vide infra, it does provide the advantage of gaining ^{13}C-labelling at two sites in **1** and **4** and at four sites in **2** and **3**. We elected to prepare a ^{13}C-allylic



Scheme 4. Synthetic routes employed for the preparation of ^{13}C-labelled dimethyl hept-1,6-dienyl-4,4-dicarboxylate **9** and ^{13}C,^2H-labelled **10** and **11**

ester since this should be readily isolable and shelf stable and could then be coupled to either dimethyl malonate or to dimethyl allyl malonate (**15**) under the standard Pd-catalysed allylic alkylation conditions.[21] So that the allylic electrophile would not be inconveniently volatile, but could also be readily distilled if necessary, we decided to prepare a benzoate ester. Furthermore, since ^{13}C-labelled formaldehyde (or paraformaldehyde) is rather expensive, we chose to label C(3) using a Wittig reaction (with phosphonium salt derived from $^{13}CH_3I$) rather than C(1) using a vinyl anion.[22a]

The synthesis of the aldehyde (**20**, Scheme 4) required for the Wittig reaction proved straightforward. Solketal (the 1,2-monoacetonide of glycerol) was converted into its benzoate ester (71%), the acetal hydrolysed (92%) and then the diol oxidatively cleaved with periodate to give **20** in 59% yield. Using $[Ph_3PCH_3][I]$ as ylide precursor, it took some while to find a method for the successful methylenation of **20**.[23] The first trace of allyl benzoate (< 5%) was observed when we employed KH with 18-crown-6 in THF. Switching to KHMDS in THF gave a marked improvement and isolable quantities of allyl benzoate were obtained. However, conditions were found to be crucial since even though aldehyde **20** reacted almost instantly with the ylide at −68 °C (the bright yellow colour is discharged), if the reaction is then quenched the yield of allyl benzoate is only 32%. Changing solvent to toluene or ether gave no real improvement and no other identifiable products are isolated. However, if the reaction is conducted at −10 °C and then allowed to warm to ambient temperature before quenching, the yield is much improved (67%). We assume that the collapse of what is presumably the betaine intermediate is slow. Using these conditions and generating the ylide from $[Ph_3P^{13}CH_3][I]$ we obtained [3-$^{13}C_1$]allyl benzoate (**21**) (> 99% ^{13}C) in good yield. Unfortunately, [3,3-$^2H_2$]allyl benzoate (**22**) prepared analogously from $[Ph_3P^{13}CD_3][I]$ (> 98% D_3) was obtained with low deuterium incorporation (70% D_2, 29% D_1, 1% D_0).[24]

With ^{13}C-labelled allyl benzoate in hand, preparation of the ^{13}C-labelled diallylmalonates **9**, **10**, and **11** was readily achieved. Using Pd_2dba_3·dba and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) as ligand in THF (1 mol-% Pd), the sodium salt of dimethyl malonate reacted rapidly with [3-$^{13}C_1$]-**21** to give [1,3-$^{13}C_1$]-labelled allylmalonate **23** in 88% yield. Selective reductions of dimethyl propargylmalonate, as Scheme 2, gave [$^2H_1$]-**24** and [(*E*)-$^2H_1$]-**25**. The anions of

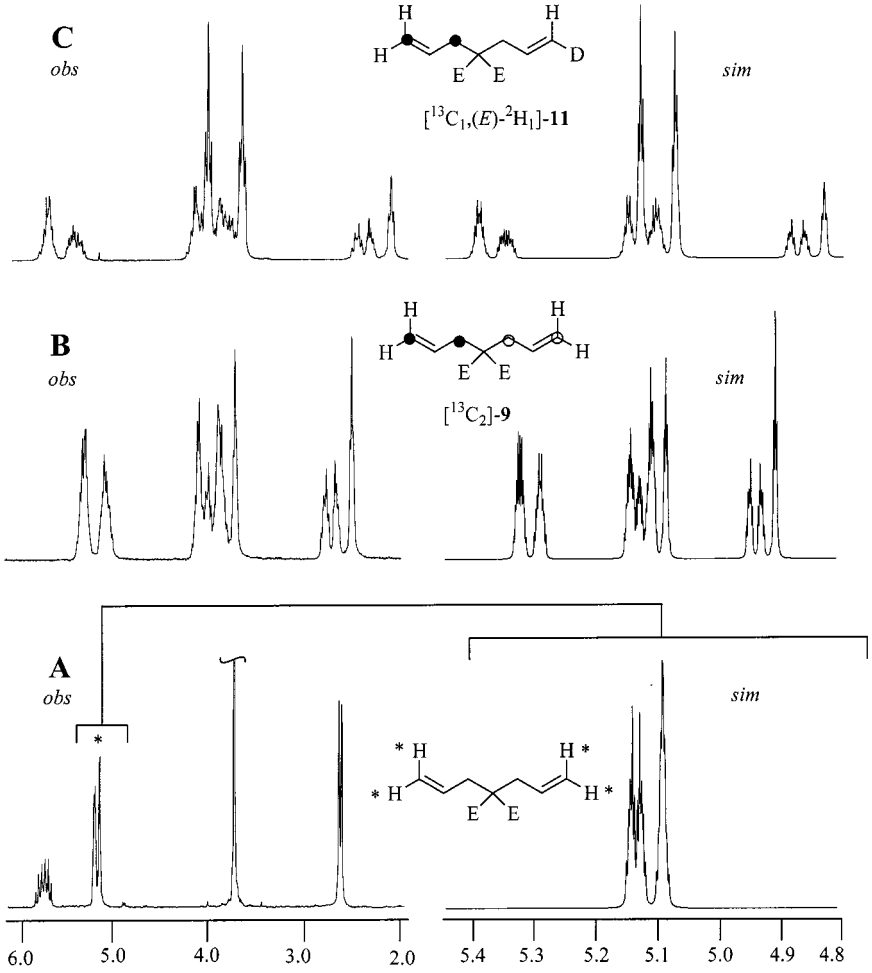


Figure 1. **A**: The ^1H NMR (300 MHz, $CDCl_3$) spectrum of dimethyl hept-1,6-dienyl-4,4-dicarboxylate (**1**) and simulated ('*sim*') subspectrum of the terminal alkene protons. Spectra **B** and **C**: observed and simulated sub-spectra of dimethyl [1,3-$^{13}C_1$,5,7-$^{13}C_1$]hept-1,6-dienyl-4,4-dicarboxylate (**9**, 400 MHz) and dimethyl [1,3-$^{13}C_1$,7-(*E*)-$^2H_1$]hept-1,6-dienyl-4,4-dicarboxylate (**11**, 300 MHz)

23, **24**, and **25** were treated, again under Pd-catalysis, with [3-$^{13}C_1$]-**21** to give doubly labelled products [$^{13}C_2$]-**9**, [$^{13}C_1$,$^2H_1$]-**10** and [$^{13}C_1$,(*E*)-$^2H_1$]-**11** in moderate to good yields.

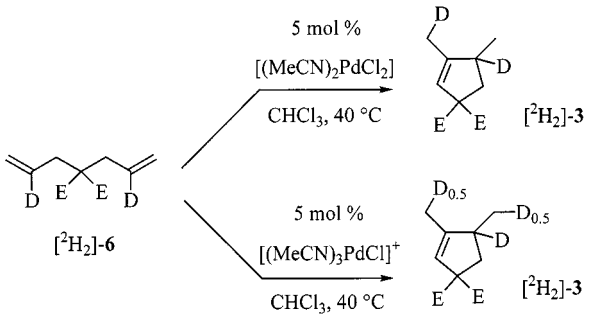
^{1}H NMR *Spectra of Labelled Substrates*

Although quantitation of the ^{2}H-label incorporation was performed by integration of ^{1}H NMR signals (and supported by MS analyses, ^{2}H NMR and ^{13}C NMR), the incorporation of the various isotopic labels in [(*E,E*)-$^2H_2$]-**5**, [$^2H_2$]-**6**, [(*Z,Z*)-$^2H_2$]-**7**, [$^2H_6$]-**8**, [$^{13}C_2$]-**9**, [$^{13}C_1$,$^2H_1$]-**10**, and [$^{13}C_1$-(*E*)-$^2H_1$]-**11** causes considerable changes in the ^{1}H NMR spectra as compared to unlabelled **1**.

In particular the *mutually exclusive* 50% ^{13}C-incorporation in the allyl chain, arising through essentially symmetrical [Pd-π-^{13}C-allyl] intermediates, results in complicated mixtures. To confirm the isotopic labelling patterns in the non-symmetrically labelled compounds [$^{13}C_2$]-**9**, [$^{13}C_1$,$^2H_1$]-**10**, and [$^{13}C_1$ (*E*)-$^2H_1$]-**11**, we simulated their ^{1}H NMR spectra. The following simplifications and methods were employed: a) δ_H, δ_C, and $J_{H,H}$ values were extracted (directly or by simulation) from NMR analysis of unlabelled **1**; b) $^1J_{C,H}$ values were extracted directly from ^{1}H NMR spectra, and 'normal' $^nJ_{C,H}$ and $^nJ_{C,C}$ values ($n > 1$) were employed;[25] c) $J_{X,D}$ were predicted by using the approximation $J_{X,D} \approx [(J_{X,H})/6.5]$;[25] d) isotope shifts were obtained by iteration and e) we treated any carbon with 50% ^{13}C incorporation as two separate species, one with 100% ^{13}C and one with 0%. The simulated spectra correlated quite well with the observed ^{1}H NMR spectra, see for example sub-spectra for the terminal alkene protons in [$^{13}C_2$]-**9** and [$^{13}C_1$,(*E*)-$^2H_1$]-**11** − Figure 1.

Conclusions

We have developed reliable and practical synthetic routes for the synthesis of six isotopically labelled variants of **1** (namely, [(*E,E*)-$^2H_2$]-**5**, [$^2H_2$]-**6**, [(*Z,Z*)-$^2H_2$]-**7**, [$^2H_6$]-**8**, [$^{13}C_2$]-**9**, [$^{13}C_1$,$^2H_1$]-**10**, and [$^{13}C_1$-(*E*)-$^2H_1$]-**11**) in a state of high purity. The initial synthetic strategy involved introduction of the ^{13}C-labels via a Wittig-type methylenation of aldehyde **16**. However, this failed to react with a variety of ylides − even at reflux in THF. Consequently we changed strategy and utilised α-benzoyloxy aldehyde **20** (Scheme 4).



Scheme 5. Deployment of [$^2H_2$]-**6** to demonstrate mechanistic differences between neutral and cationic chloropalladium catalysts for the regioselectiove cycloisomerisation of **1** to **3**

In contrast to **16**, aldehyde **20** reacted rapidly with $Ph_3P{=}CH_2$ − even at −68 °C. However, only when the ylide was generated from KHMDS and then the betaine warmed to 20 °C did this yield the desired allyl benzoate. Nonetheless, under these optimised conditions, good yields of ^{13}C-labelled allyl benzoate [$^{13}C_1$]-**21** are obtained and this can be smoothly coupled to malonate units via Pd-catalysed allylic alkylation reactions. The use of a symmetrical ^{13}C-labelled Pd-π-allyl intermediate provides the advantage that the ^{13}C-label is introduced at *two* sites [C(1) and C(3)] in **1** − although the resulting *mutually exclusive* 50% incorporation at each site does slightly complicate ^{1}H NMR spectra. In parallel we have developed high yielding ^{2}H-labelling methods which thereby allow preparation of single (^{2}H) and mixed (^{13}C, ^{2}H) label systems with defined regiochemistry and alkene geometry.

In summary, six isotopically labelled variants of **1** are readily prepared and are useful probes in the study of the mechanism of catalysed cycloisomerisation reactions.[12] For example, Pd-catalysed cycloisomerisation of **1** by neutral[26] and cationic[7] chloropalladium nitrile complexes ([$(MeCN)_2PdCl_2$] and [$(MeCN)_3PdCl$][OTf] respectively) gives **3** with good regioselectivity. Use of [$^2H_2$]-**6**, which affords [$^2H_2$]-**3**, reveals that these two catalysts are mechanistically distinct − Scheme 5.[27] Additionally, Pd^0 complexes of 1,6-dienes have recently attracted attention since they can provide useful sources of "naked metals"[28] and the NMR characterisation of analogous Pd^{II} complexes of the diene **1** is greatly faciliated by isotopic substitution.[27] Furthermore, the ^{13}C-labelled allyl benzoate [$^{13}C_1$]-**21** may prove of utility in other synthetic strategies including metal-allyl chemistry.

Experimental Section

General: Solvents and reagents were purified by standard procedures. Anhydrous solvents were purchased from Fluka or Aldrich and used as received. $^{13}CH_3I$ (>99% ^{13}C) was purchased from Promochem and from Aldrich, MeOD (99% D) and D_2O (99.9% D) were purchased from Aldrich and from Goss Scientific, $Cp_2Zr(Cl)D$ was purchased from Fluka. Material supplied by Aldrich was found to be completely inactive. KHMDS (0.5 M in toluene) was purchased from Fluka. [$PPh_3{}^{13}CH_3$][I] was prepared in essentially quantitative yield by collection of the crystalline material deposited from reaction of stoichiometric quantities of PPh_3 and $^{13}CH_3I$ in toluene. Dimethyl allylmalonate [dimethyl but-3-ene-1,1-dicarboxylate] was purchased from Lancaster Synthesis. A mixture of dimethyl propargylmalonate [dimethyl but-3-yne-1,1-dicarboxylate] and dimethyl (dipropargyl)malonate [dimethyl hept-1,6-dienyl-4,4-dicarboxylate] was prepared by reaction of dimethyl malonate with NaH and excess propargyl bromide in THF. The two components were separated column chromatography. α-Benzoyloxy acetaldehyde was prepared according to a literature procedure.[29] When appropriate, reactions were carried out under nitrogen using standard Schlenk techniques. − NMR experiments were performed on JEOL instruments (Delta 270, Lambda 300, GX400, and Eclipse 400). NMR spectra were recorded in $CDCl_3$ or in $CHCl_3$. ^{1}H NMR spectra were referenced internally to residual $CHCl_3$ ($\delta = 7.27$) or to TMS ($\delta = 0.00$). ^{2}H NMR spectra were

referenced internally to $CDCl_3$ (δ = 7.27, ca. 1% added to $CHCl_3$). ^{13}C NMR spectra were referenced to $CDCl_3$ (δ = 77.0). in ^{13}C NMR spectra of labelled compounds, when appropriate, satellites are reported and are denoted as '*sat*'. Spectral simulation (^1H) was performed using *g* NMR software. Coupling constants extracted in such a manner are reported as *'simul.'*. − Mass spectra were obtained using both CI and EI sources on a Fisons 'Micromass Autospec' mass spectrometer. − Flash column chromatography: Merck silica gel 60. − TLC: 0.25 mm, Merck silica gel 60 F254 visualising at 254 nm or with acidic (H_2SO_4) aq. $KMnO_4$ solution (ca. 2%).

Dimethyl [1,7-$^2H_2$]Hept-1,6-diynyl-4,4-dicarboxylate (14): NaOMe (17 mg, 0.3 mmol) was added to a stirred solution of dimethyl hept-1,6-diynyl-4,4-dicarboxylate (368 mg, 1.77 mmol) in MeOD (5 cm^3). After 0.5 h the mixture was concentrated in vacuo to 1 cm^3 and fresh MeOD (5 cm^3) was added. The cycle was repeated three times after which the mixture was concentrated in vacuo, D_2O (2 cm^3) was added and then the mixture extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were washed with D_2O (2 cm^3), dried with anhydrous $MgSO_4$ and concentrated in vacuo to afford the title compound (254 mg, 68%) as a white solid. >99% D_2 (^1H NMR). − δ_H (400 MHz, $CDCl_3$): 3.00 (s, 4 H, CH_2), 3.77 (s, 6 H, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 22.6 (CH_2), 53.1 (CH_3), 56.4 (CE_2), 71.5 (*t*, $^1J_{CD}$ 38.4, *C*D), 77.8 (*t*, $^2J_{CD}$ 7.7, CH_2CCD), 169.0 (CO_2); δ_D (46 MHz, $CHCl_3$): 2.04 (s); *m*/*z* (CI): 211 [MH^+] (10%), 202 (13), 197 (12), 187 (52), 178 (42), 170 (42), 170 (40), 151 (46), 123 (64), 119 (100), 109 (62), 105 (44).

Dimethyl [1,7-(*E,E*)-$^2H_2$]Hept-1,6-dienyl-4,4-dicarboxylate (5): To a stirred mixture of dimethyl hept-1,6-diynyl-4,4-dicarboxylate (150 mg, 0.72 mmol) in CH_2Cl_2 (5 cm^3) was added $Cp_2Zr(Cl)H$ (516 mg, 2.00 mmol) at 0 °C. After 80 min at 0 °C the mixture was quenched by the addition of D_2O (2 cm^3). The solution was filtered through a pad of silica, eluted with CH_2Cl_2 (3 × 5 cm^3) and then concentrated in vacuo. Purification by column chromatography using hexane/ethyl acetate (5:1) as the eluent afforded **5** as a colourless oil (124 mg, 80%). > 96% D_2 (^1H NMR). − δ_H (400 MHz, $CDCl_3$): 2.64 (d, 4 H, ^3J 8.0, CH_2CH=), 3.72 (s, 6 H, CH_3), 5.10 (d, 2 H, $^3J_{trans}$ 16.0, CH=C*H*D), 5.64 (d*t*, 2 H, $^3J_{trans}$ 16.0, ^3J 8.0, C*H*=CHD); δ_C (100 MHz, $CDCl_3$): 36.9 (*C*H_2CH=), 52.4 (CH_3), 57.6 (CE_2), 118.9 (*t*, J_{CD} 23.8, CH=*C*HD), 132.1 (*C*H=CHD), 171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.15 (s); *m*/*z* (CI): 215 [MH^+] (42%), 214 [M^+] (45), 213 [$M^+ - H$] (27), 212 [$M^+ - D$] (21), 199 (28), 197 (29), 172 (25), 140 (100).

Dimethyl [2,6-$^2H_2$]Hept-1,6-dienyl-4,4-dicarboxylate (6): Following the procedure for **5**, dimethyl hept-1,6-diynyl-4,4-dicarboxylate (206 mg, 0.99 mmol) was treated with $Cp_2Zr(Cl)D$ (716 mg, 2.77 mmol) and quenched with H_2O to give **6** (144 mg, 68%) as a colourless oil. > 99% D_2 (^1H NMR). − δ_H (400 MHz, $CDCl_3$): 2.64 (s, 4 H, CH_2CD=), 3.72 (s, 6 H, CH_3), 5.10 (br. s, 4 H, =CH_2); δ_C (100 MHz, $CDCl_3$): 36.8 (*C*H_2CD=), 52.4 (CH_3), 57.6 (CE_2), 119.0 (=CH_2), 131.9 (*t*, $^1J_{CD}$ 23.8, *C*D=CH_2), 171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.68 (s); *m*/*z* (EI): 214 [M^+] (3%), 183 (6), 172 (26), 154 (24), 140 (100), 123 (18).

Dimethyl [1,7-(*Z,Z*)-$^2H_2$]Hept-1,6-dienyl-4,4-dicarboxylate (7): Following the procedure for **5**, **14** (206 mg, 0.99 mmol) was treated with $Cp_2Zr(Cl)H$ (657 mg, 2.55 mmol) and quenched with H_2O to give **7** (136 mg, 74%) as a colourless oil. > 99% D_2 (^1H NMR). − δ_H (400 MHz, $CDCl_3$): 2.57 (d, 4 H, ^3J 7.3, CH_2CH=), 3.72 (s, 6 H, CH_3), 5.10 (2 H, $^3J_{cis}$ 10.3, CH=C*H*D), 5.52−5.61 (m, 2 H, C*H*=CHD); δ_C (100 MHz, $CDCl_3$): 36.9 (*C*H_2CH=), 52.4 (CH_3), 57.6 (CE_2), 118.9 (*t*, $^1J_{CD}$ 23.8, CH=*C*HD), 132.1 (*C*H=CHD), 171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.14 (br. s); *m*/*z* (CI): 215 [MH^+] (23%), 187 (61), 155 (33), 143 (30), 83 (100), 57 (20).

Dimethyl [1,1,2,6,7,7-$^2H_6$]Hept-1,6-dienyl-4,4-dicarboxylate (8): Following the procedure for **5**, **14** (185 mg, 0.88 mmol) was treated with $Cp_2Zr(Cl)D$ (576 mg, 2.22 mmol) and quenched with D_2O to give **8** (159 mg, 83%) as a colourless oil. >97% 4,4′-D_2; > 96% 5,5,5′,5′-D_4 (^1H NMR). − δ_H (400 MHz, $CDCl_3$): 2.64 (s, 4 H, CH_2), 3.72 (s, 6 H, CH_3); δ_C (100 MHz, $CDCl_3$): 36.7 (CH_2), 52.3 (CH_3), 57.6 (CE_2), 118.8 (sp, $^1J_{CD}$ 24.6, CD=*C*D$_2$), 131.7 (*t*, $^1J_{CD}$ 23.83, *C*D=CD$_2$), 171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.13 (s, 2 D, CD=C*D*$_2$), 5.68 (s, 1 D, C*D*=CD$_2$); *m*/*z* (CI^+): 219 [MH^+] (2%), 218 [M^+] (5), 187 (19), 159 (44), 142 (30), 127 (39), 111 (40), 97 (67), 85 (65), 71 (74), 57 (100).

Dimethyl [3-$^2H_1$]But-3-ene-1,1-dicarboxylate (24): Following the procedure for **5**, dimethyl but-3-yne-1,1-dicarboxylate (302 mg, 1.78 mmol) was treated with $Cp_2Zr(Cl)D$ (697 mg, 2.69 mmol) and quenched with H_2O to give **24** (207 mg, 67%) as a colourless oil. > 99% D (^1H NMR). − δ_H (300 MHz, $CDCl_3$): 2.65 (d, 2 H, ^3J 7.5, CH_2CD=), 3.46 (t, 1 H, ^3J 7.5, C*H*CH_2), 3.74 (s, 6 H, CH_3), 5.05−5.15 (m, 2 H, =CH_2); δ_C (75 MHz, $CDCl_3$): 32.7 (*C*H_2CD=), 51.4 (CH_3), 52.5 (HCE_2), 117.5 (=CH_2), 133.6 (*t*, $^1J_{CD}$ 23.6, *C*D=CH_2), 169.3 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.80 (s); *m*/*z* (CI^+): 174 [MH^+] (34%), 149 (11), 142 (73), 114 (15), 110 (29), 88 (67), 84 (110).

Dimethyl [4-(*E*)-$^2H_1$]But-3-ene-1,1-dicarboxylate (25): Following the procedure for **5**, dimethyl but-3-yne-1,1-dicarboxylate (403 mg, 2.37 mmol) was treated with $Cp_2Zr(Cl)H$ (850 mg, 3.29 mmol) and quenched with D_2O to give **25** (238 mg, 58%) as a colourless oil. > 94% D (^1H NMR). − δ_H (300 MHz, $CDCl_3$): 2.67 (*ddd*, 2 H, ^3J 7.4, 7.1, ^4J 1.5, CH_2CH=), 3.47 (t, 1 H, ^3J 7.4, *H*CCH_2), 3.74 (s, 6 H, CH_3), 5.12 (*dt*, 1 H, $^3J_{trans}$ 17.0, ^4J 1.5, C*H*D), 5.77 (*dt*, 1 H, ^3J 7.1, $^3J_{trans}$ 17.0, C*H*=CHD); δ_C (75 MHz, $CDCl_3$): 32.8 (*C*H_2CH=), 51.3 (HCE_2), 52.4 (CH_3), 117.3 (*t*, $^1J_{CD}$ 24.8, *C*HD), 133.7 (*C*H=CHD), 169.2 (CO_2); δ_D (46 MHz: $CHCl_3$): 5.00 (s); *m*/*z* (CI): 174 [MH^+] (20), 149 (16), 142 (40), 125 (28), 115 (18), 114 (24), 97 (26), 71 (36), 61 (16), 59 (14), 57 (52).

[3-$^{13}C_1$]Allyl Benzoate (21): A 0.5 M solution of $KN(SiMe_3)$ (11.4 cm^3, 5.7 mmol) was added dropwise to a suspension of [$PPh_3P^{13}CH_3$][I] (2.31 g, 5.70 mmol) in THF (30 cm^3) at −10 °C and the bright yellow suspension was then stirred for 2 h. Benzoyloxyacetaldehyde (850 mg, 5.18 mmol) in THF (2 cm^3) was then added, the reaction mixture allowed to warm to room temp. and then stirred for 3 h. After quenching with water (10 cm^3), the mixture was extracted with diethyl ether (3 × 20 cm^3). The combined extracts washed with brine (10 cm^3), dried with anhydrous magnesium sulfate, and concentrated in vacuo to yield a yellow oil. Purification by column chromatography using hexane/ethyl acetate (20:1) as the eluent afforded **21** (556 mg, 67%) as a colourless oil. − δ_H (300 MHz, $CDCl_3$): 4.83 (*ddt*, 2 H, ^3J 5.6, $^3J_{CH}$ 11.2, ^4J 1.5, CH_2CH=), 5.25 (*dddt*, 1 H, $^1J_{CH}$ 159.6, ^2J 1.5, $^3J_{cis}$ 10.4, ^4J 1.5, ^{13}C*H*H), 5.41 (*dddt*, 1 H, $^1J_{CH}$ 155.5, ^2J 1.5, $^3J_{trans}$ 17.3, ^4J 1.5, ^{13}C*H*H), 6.04 (*ddt*, 1 H, ^3J 5.6, $^3J_{cis}$ 10.4, $^3J_{trans}$ 17.3, C*H*=), 7.41−7.50 (m, 2 H, *m*-CHaryl), 7.53−7.61 (m, 1 H, *p*-CHaryl), 8.04−8.10 (m, 2 H, *p*-CHaryl); δ_C (75 MHz, $CDCl_3$): 65.5 (*C*H_2CH=), 118.2 (=$^{13}CH_2$), 128.3 (*m*-CHaryl), 129.6 (*o*-CHaryl), 132.6 (*d*, $^1J_{CC}$ 70.2, *C*H=^{13}C), 132.9 (*p*-CHaryl), 135.3 (*i*-Caryl), 166.2 (CO_2); *m*/*z* (EI): 163 [M^+] (17%), 118 (8), 105 (100), 86 (32), 84(46), 77 (60).

Dimethyl [2,4-$^{13}C_1$]But-3-ene-1,1-dicarboxylate (23): To a stirred suspension of sodium hydride (49 mg, 2.02 mmol) in THF (4 cm^3) was added dimethylmalonate (0.21 mL, 1.84 mmol) at 0 °C. After

15 min a solution of dppf (15 mg, 1.5 mol-%) and Pd_2·dba_3·dba (17 mg, 1 mol-% Pd) in THF (1 cm^3) was added, followed by **21** (300 mg, 1.84 mmol). After 2 h the mixture was quenched by the addition of 2.8 M NH_4Cl aq. (10 cm^3) and extracted with ethyl acetate (3 × 20 cm^3). The combined extracts were washed with brine (10 cm ^{3}), dried with anhydrous magnesium sulfate, and concentrated in vacuo to yield a brown oil. Purification by column chromatography using hexane/ethyl acetate (6:1) as the eluent gave **23** (284 mg, 88%) as a colourless oil. − δ_H (300 MHz, $CDCl_3$): 2.65 (*dddt*, 2 H, ^3J 7.3, 7.3, $^3J_{CH}$ 6.8, ^4J 1.2, CH_2CH=, and *dddt*, $^1J_{CH}$ 131.7, ^3J 7.3, 7.3, ^4J 1.2, ^{13}CH_2CH=), 3.47 (t, 1 H, ^3J 2.0, HCCH_2, and *dt*, $^2J_{CH}$ 15.2, ^3J 2.0, HC^{13}CH_2), 3.72 (*s*, 6 H, CH_3), 5.08 (*dddd*, H, ^2J 1.2, ^3J 10.3, ^4J 1.2, $^3J_{CH}$ 10.3, =CH$H_{cis,}$ and *dddd*, $^1J_{CH}$ 158.3, ^2J 1.2, ^3J 10.3, ^4J 1.2, =^{13}CHH_{cis}), 5.12 (*dddd*, H, ^2J 1.2, ^3J 17.1, ^4J 1.2, $^3J_{CH}$ 7.3, =CHH_{trans}, and *dddd*, $^1J_{CH}$ 154.4, ^2J 1.2, ^3J 17.1, ^4J 1.2, =^{13}CHH_{trans}), 5.77 (*ddt*, 1 H, ^3J 17.1, 10.3, 7.3, C*H*=CH_2); δ_C (100 MHz, $CDCl_3$): 32.9 (*sat*: $^1J_{CC}$ 33.0 and 42.3, ^{13}*C*H_2CH=), 51.4 (*d*, $^1J_{CC}$ 33.0, H*C*$E_2^{13}CH_2$), 51.4 (*d*, $^3J_{CC}$ 3.1, H*C*E_2CH_2), 52.5 (CH_3), 117.7 (*sat*: $^1J_{CC}$ 70.0, CH=^{13}*C*H_2), 133.9 (*d*, $^1J_{CC}$ 70.0, *C*H=$^{13}CH_2$), 133.9 (*d*, $^1J_{CC}$ 42.3 $^{13}CH_2$*C*H=), 169.3 (CO_2); *m*/*z* (EI$^+$): 172 [M$^+$] (14%), 155 (66), 140 (33), 123 (57), 95 (84), 84 (100), 71 (38), 57 (64).

Dimethyl [1,3-$^{13}C_1$,5,7-$^{13}C_1$]Hept-1,6-dienyl-4,4-dicarboxylate (9): Following a procedure analogous to that outlined for **23**, **21** (256 mg, 1.57 mmol) was treated with **23** (272 mg, 1.57 mmol) to give **9** as a colourless oil (64 mg, 19%). − δ_H (400 MHz, $CDCl_3$):: 2.64 (4 H, $^3J_{CH}$ 6.7, ^3J 7.4, ^4J 1.1, $E_2C(CH_2CH^{13}CH_2)_2$ and *ddt*, $^1J_{CH}$ 132.0, ^3J 7.4, ^4J 1.1, $^{13}CH_2CHCH_2CE_2{}^{13}CH_2$, and *dddt*, $^1J_{CH}$ 132.0, $^3J_{CH}$ 5.0, ^2J 7.4, ^4J 1.1, $^{13}CH_2CE_2{}^{13}CH_2$, and *dddt*, $^3J_{CH}$ 6.7, $^3J_{CH}$ 5.0, ^3J 7.4, ^4J 1.1, $^{13}CH_2CE_2CH_2CH=^{13}CH_2$); 3.72 (*s*, 6 H, CH_3), 5.12 (2 H, *dddt*, $^2J_{simul.}$ 1.8, $^3J_{cis}$ 9.9, ^4J 1.1, $^3J_{CH}$ 12.7, CH=C*H*H, and *dddt* $^1J_{CH}$ 158.0, $^2J_{simul.}$ 1.8, $^3J_{simul.}$ 9.9, ^4J 1.1, CH=^{13}C*H*H), 5.13 (2 H, *dddt*, $^1J_{CH}$ 154.0, $^2J_{simul.}$ 1.8, $^3J_{trans\ simul}$, 16.8, ^4J 1.1, CH=^{13}CH*H*, and *dddt*, $^2J_{simul.}$ 1.8, $^3J_{trans\ simul.}$ 16.8, $^3J_{CH}$ 7.6, ^4J 1.1, CH=CH*H*); 5.65 (2 H, *dddt*, $^3J_{cis\ simul.}$ 9.9, $^3J_{trans\ simul.}$ 16.8, ^3J 7.4, $^2J_{CH}$ 5.0, $^{13}CH_2CH$=CH_2, and *dddt*, $^3J_{cis\ simul.}$ 9.9, $^3J_{trans\ simul.}$ 1.8, ^3J 7.4, $^2J_{CH}$ 0.4, C*H*$^{13}CH_2$); δ_C (100 MHz, $CDCl_3$): 36.9 (*sat*: $^1J_{CC}$ 33.8 and 43.0, ^{13}*C*H_2CH=), 52.4 (CH_3), 57.7 (*dd*, $^1J_{CC}$ 33.8, $^3J_{CC}$ 3.1, CE_2), 119.2 (*sat*: $^1J_{CC}$ 69.2, CH=^{13}*C*H_2), 132.2 (*d*, $^1J_{CC}$ 43.0, $^{13}CH_2$*C*H=), 132.2 (*d*, $^1J_{CC}$ 69.2,*C*H=$^{13}CH_2$), 171.2 (CO_2).

Dimethyl [1,3-$^{13}C_1$,6-$^2H_1$]Hept-1,6-dienyl-4,4-dicarboxylate (10): Following a procedure analogous to that outlined for **23**, **21** (175 mg, 1.08 mmol) was treated **24** (186 mg, 1.08 mmol) to give **10** (100 mg, 43%) as a colourless oil. > 99% D (^{1}H NMR). − δ_H (300 MHz, $CDCl_3$): 2.64 (*dt*, 4 H, $^3J_{DH\ simul.}$ 1.1, ^4J 1.1, CH_2CD=, and *ddt*, $^1J_{CH}$ 132.0, ^3J 7.4, ^4J 1.1, ^{13}CH_2CH=, and *ddt*, ^3J 7.4, $^3J_{CH}$ 6.7, ^4J 1.1, CH_2CH=$^{13}CH_2$, and *ddt*, $^3J_{DH\ simul.}$ 1.1, $^3J_{CH}$ 5.0, ^4J 1.10, $^{13}CH_2CE_2CH_2$CD=), 3.72 (s, 6 H, CH_3), 5.11 (*ddt*, 2 H, $^2J_{simul.}$ 1.8, $^3J_{HD\ simul.}$ 1.5, ^4J 1.1, CD=C*H*H, and *dddt*, $^1J_{CH}$ 158.0, $^2J_{simul.}$ 1.8, $^3J_{cis\ simul.}$ 9.9, ^4J 1.1, CH=^{13}C*H*H, and *dddt*, $^2J_{simul.}$ 1.8, $^3J_{cis\ simul.}$ 9.90, $^3J_{CH}$ 12.7, ^4J 1.1, $^{13}CH_2$CH=C*H*H), 5.12 (*ddt*, 2 H, $^2J_{simul.}$ 1.8, $^3J_{DH\ simul.}$ 2.6, ^4J 1.1, CD=C*H*H, and *dddt*, $^1J_{CH}$ 154.0, $^2J_{simul.}$ 1.8, $^3J_{trans\ simul.}$ 16.8, ^4J 1.1, CH=^{13}C*H*H, and *dddt*, $^2J_{simul.}$ 1.8, $^3J_{trans\ simul.}$ 16.8, $^3J_{CH}$ 7.6, ^4J 1.1, $^{13}CH_2$CH=C*H*H), 5.65 (*dddt*, 1 H, $^2J_{CH\ simul.}$ 0.4, ^3J 7.4, $^3J_{cis\ simul.}$ 9.9, $^3J_{trans\ simul.}$ 16.8, C*H*=$^{13}CH_2$, and *dddt*, $^2J_{CH}$ 5.0, ^3J 7.4, $^3J_{cis\ simul.}$ 9.9, $^3J_{trans\ simul.}$ 16.8, $^{13}CH_2$C*H*=), δ_C (75 MHz, $CDCl_3$): 36.9 (*C*H_2CE_2), 52.4 (CH_3), 59.7 (CE_2), 119.2 (CH=^{13}*C*H_2, CD=*C*H_2, $^{13}CH_2$CH=*C*H_2), 131.9 (*t*, $^1J_{CD}$ 69.6, *C*D=CH_2), 132.0 (*C*H=$^{13}CH_2$, $^{13}CH_2$*C*H=), 171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.69 (s); *m*/*z* (EI): 215 [MH$^+$] (2%), 183 (3), 172 (2), 155 (7), 151 (6), 140 (4), 123 (5), 105 (4), 95 (6), 86 (64), 84 (100).

Dimethyl [1,3-$^{13}C_1$,7-(*E*)-$^2H_1$]Hept-1,6-dienyl-4,4-dicarboxylate (11): Following a procedure analogous to that outlined for **23**, **21** (215 mg, 1.32 mmol) was treated with **25** (228 mg, 1.32 mmol) to give **11** (216 mg, 76%) as a colourless oil. > 94% D (^{1}H NMR). − δ_H (300 MHz, $CDCl_3$): 2.64 (*ddd*, 4 H, ^3J 7.4, ^4J 1.1, $^4J_{DH\ simul.}$ 0.2, $^{13}CH_2$=CHCH_2CH_2, and *ddt* ^3J 7.4, $^3J_{CH}$ 6.7, ^4J 1.1 CH_2CH=$^{13}CH_2$, *ddt* ^3J 7.4, ^4J 1.1 $^1J_{CH}$ 132.0, ^{13}CH_2CH=, and *dddd*, $^3J_{CH}$ 5.0, ^3J 7.4, ^4J 1.1, $^4J_{DH\ simul.}$ 0.2, $^{13}CH_2$=CHCH_2), 3.72 [s, 6 H, $C(CO_2CH_3)_2$], 5.11 (*dddt*, 1 H, $^2J_{simul.}$ 1.8, $^3J_{cis\ simul.}$ 9.9, ^4J 1.1, $^1J_{CH}$ 158.0, CH=^{13}C*H*H, and *dddt* $^2J_{simul.}$ 1.8, $^3J_{CH}$ 12.7, $^3J_{cis\ simul.}$ 9.9, ^4J 1.1, $^{13}CH_2$CH=C*H*H), 5.12 (*dddt*, 2 H, $^1J_{CH}$ 154.0, $^2J_{simul.}$ 1.8, $^3J_{trans\ simul.}$ 16.8, ^4J 1.1, CH=^{13}C*H*H, and *dddt* $^2J_{simul.}$ 1.8, $^3J_{trans\ simul.}$ 16.8, $^3J_{CH}$ 7.6, ^4J 1.1, $^{13}CH_2$CH=C*H*H, and *ddt* $^2J_{DH\ simul.}$ 0.3, $^3J_{trans\ simul.}$ 16.8, ^4J 1.1, CH=C*H*D), 5.65 (*dddt*, 2 H, $^2J_{CH\ simul.}$ 0.4, $^3J_{trans\ simul.}$ 16.80, $^3J_{cis\ simul.}$ 9.9, ^3J 7.4, C*H*=$^{13}CH_2$, and *dddt* $^2J_{CH\ simul.}$ 5.0, $^3J_{cis\ simul.}$ 9.9, $^3J_{trans\ simul.}$ 16.8, ^3J 7.4, $^{13}CH_2$C*H*=, and *ddt*, ^3J 7.4, $^3J_{trans\ simul.}$ 16.8, $^3J_{DH\ simul.}$ 1.5, C*H*=CDH); δ_C (75 MHz, $CDCl_3$): 36.6 (*C*H_2CH=CHD, ^{13}*C*H_2CH=, *C*H_2CH=$^{13}CH_2$) 52.4 (CH_3), 57.7 (CE_2), 119.3 (CH=^{13}*C*H_2, $^{13}CH_2$CH=*C*H_2), 119.0 (*t*, $^1J_{CD}$ 19.3, CH=*C*HD), 132.1 (*d*, $^1J_{CC}$ 69.6, *C*H=$^{13}CH_2$), 132.1 (*C*H=CHD), 132.3 (*d*, $^1J_{CC}$ 42.9, $^{13}CH_2$*C*H=),171.2 (CO_2); δ_D (46 MHz, $CHCl_3$): 5.14 (s); *m*/*z* (EI): 215 [MH$^+$] (33%), 183 (41), 172 (8), 155 (66), 151 (40), 123 (43), 95 (38), 84 (100), 79 (85), 63 (29), 57 (16).

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[1] Reviews: [1a]B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34−42. − [1b] B. M. Trost, M. J. Krische, *Synlett* **1998**, 1−15.
[2] A. Bright, J. F. Malone, J. K. Nicholson, J. Powell, B. L. Shaw, *J. Chem. Soc., Chem. Commun.* **1971**, 712−713.
[3] [3a] R. Grigg, T. R. B. Mitchell, A. Ramasubbu, *J. Chem. Soc., Chem. Commun.* **1979**, 669−670. − [3b] R. Grigg, T. R. B. Mitchell, A. Ramasubbu, *J. Chem. Soc., Chem. Commun.* **1980**, 27−28. − [3c] R. Grigg, J. F. Malone, T. R. B. Mitchell, A. Ramasubbu, R. M. Scott, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1745−1754.
[4] E. Schmitz, R. Urban, G. Zimmermann, *J. Prakt. Chem.* **1976**, *318*, 185; E. Schmitz, U. Hench, D. Habisch, *J. Prakt. Chem.* **1976**, *318*, 471.
[5] Y. Yamamoto, N. Ohkoshi, M. Kameda, K. Itoh, *J. Org. Chem.* **1999**, *64*, 2178−2179.
[6] B. Radetich, T. V. RajanBabu, *J. Am. Chem., Soc.* **1998**, *120*, 8007−8008.
[7] A. Heumann, M. Moukhliss, *Synlett* **1998**, 1211−1212.
[8] Note that cycloisomerisation is not always a desirable reaction − for example, it recently was reported to be a seriously competing side reaction (43%) in a Ru-catalysed ring-closing metathesis of *N*-tosyl diallyl amine. See: A. Fürstner, M. Liebl, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, P. H. Dixneuf, *Chem. Eur. J.* **2000**, *6*, 1847−1857.
[9] [9a] W. E. Piers, P. J. Shapiro, E. E. Bunel, J. E. Bercaw, *Synlett* **1990**, 74−84. − [9b] K. S. Knight, R. M. Waymouth, *J. Am. Chem. Soc.* **1991**, *113*, 6268−6270. − [9c] G. A. Molander, J. O. Hoberg, *J. Am. Chem. Soc.* **1992**, *114*, 3123−3126. − [9d] E.-I. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124−130. − [9e] U. M. Dzhemilev, *Tetrahedron* **1995**, *51*, 4333−4346. − [9f] J. Christoffers, R. G. Bergman, *J. Am. Chem. Soc.* **1996**, *118*, 4715−4716. − [9g] S. Thiele, G. Erker, *Chem. Ber./Recueil* **1997**, *130*, 201−207.
[10] [10a] P. Denn, L. Fensterbank, M. Malacria, *Tetrahedron Lett.* **1998**, *39*, 833−836. − [10b] D. Stein, R. Samy, R. Nouguier, D. Crich, M. P. Bertrand, *J. Org. Chem.* **1997**, *62*, 275−286. − [10c]

A. M. Bernard, P. P. Piras, P. Toriggia, *Synthesis* **1990**, 527−529.

[11] G. C. Lloyd-Jones, *Synlett* **2001**, 161−183.

[12] K. L. Bray, G. C. Lloyd-Jones, unpublished results

[13] As far as we are aware, there has only been one report of the deliberate preparation of deuterated-allyl malonates: diethyl [1,7-(*Z,Z*)-$^2H_2$]hept-1,6-diene-4,4-dicarboxylate and diethyl [4-(*Z*)-$^2H_1$]but-3-ene-1,1-dicarboxylate were prepared as a mixture by Fe-mediated reaction between dimethyl malonate and ethyl 3-[(*Z*)-$^2H_1$]propen-1-yl carbonate: [13a] Y. Xu, B. Zhou, *J. Org. Chem.* **1987**, *52*, 974−977. Additionally, diethyl [4,4,2,2-$^2H_4$]but-3-ene-1,1-dicarboxylate and diethyl [4,4,3,3,2,2-$^2H_6$]but-3-ene-1,1-dicarboxylate have been isolated as side products from reaction of [1,1,3,3-$^2H_4$]-1,3-dibromopropane and [1,1,2,2,3,3-$^2H_6$]-1,3-dibromopropane with diethyl malonate: [13b] J. A. van Zee, A. L. Kwiram, *J. Am. Chem. Soc.* **1990**, *112*, 5012−5018.

[14] J. Schwartz, J. A. Labinger, Angew. Chem., *Int. Ed. Engl.* **1976**, *15*, 333−339.

[15] S. L. Buchwald, S. J. Lamaire, R. B. Nielsen, B. T. Watson, *Organic Synth.* **1992**, *71*, 77−82.

[16] Removal of the dimethyl acetal protecting group proved very troublesome. A number of methods were tested, including H_2SO_4/wet silica-gel (see reference [10b]), oxalic acid/wet silica-gel (see reference [17a]), wet silica-gel/CH_2Cl_2 (see reference [17a]), and TsOH/CH_2Cl_2 (see reference [17b]). However, under these conditions, either there was no deprotection or complete decomposition. Eventually we found that TFA in CH_2Cl_2 (see reference [17c]) effected very clean deprotection and gave aldehyde **16** in 74% yield.

[17] [17a] F. Huet, A. Levchevallier, M. Pellet, J. M. Conia, *Synthesis* **1978**, 63−65. − [17b] M. Mikolajczyk, P. Balczewski, *Synthesis* **1987**, 659−661.[17c] R. A. Ellison, E. R. Lukenbach, C.-W. Chiu, *Tetrahedron Lett.* **1975**, 499−502.

[18] The following sets of conditions (all in THF) were tested with **16** without more than a trace (< 1%) of desired diene **1** being detectable by TLC: a) with [PPh_3CH_3][I], BuLi, −78 °C to room temp. or KO*t*Bu −78 °C to room temp., or NaH, room temp. or KH, 18-crown-6, 0 °C to room temp.; b) with $Ph_2P(O)CH_3$, NaH, 0 °C or KO*t*Bu, −78 °C to room temp.; c) with $(EtO)_2P(O)CH_3$, NaH, 0 °C or KO*t*Bu, −78 °C to room temp.

[19] For example, refluxing a THF solution of the ketone **19** with two equivalents of the ylide generated from [PPh_3CH_3][I] and BuLi gave no trace (< 1%) of the desired alkene **2**. Even though the red colour of the ylide was fully discharged after 24 h at reflux.

[20] P. J. H. Carlsen, T. Katsuki, V. S. Martin, B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936−3938.

[21] J. Tsuji, *Palladium Reagents and Catalysts*, *Innovations in Organic Synthesis*, Wiley, Chichester, UK, **1995**.

[22] As far as we are aware, there have been no reports of the use of ^{13}C-labelled allylic electrophiles in Pd-catalysed allylic alkylation in the literature, nor have any [1-$^{13}C_1$]-, [2-$^{13}C_1$]-, or [3-$^{13}C_1$]-labelled allylic esters been prepared. [$^{13}C_1$]-Allylic electrophiles have been reported: [22a] [1-$^{13}C_1$]Prop-2-en-1-ol: H. Badawi, P. Lorencak, K. W. Hillig, M. Imachi, R. L. Kuczkowski, *J. Mol. Struct.* **1987**, *162*, 247−254. − [22b] [1-$^{13}C_1$]-1-Chloroprop-2-ene: W. Kirmse, V. Zellmer, B. Goer, *J. Am. Chem. Soc.* **1986**, *108*, 4912−4917. − [22c] [2-$^{13}C_1$]-1-Bromoprop-2-ene: G. A. Olah, C. L. Jeuell, A. M. White, *J. Am. Chem. Soc.* **1969**, *91*, 3961−3962.

[23] Using BuLi as base and conducting the reaction in THF gave no trace of allyl benzoate (< 1%) even though all of **20** was consumed. Use of sodium rather than lithium containing bases (NaHMDS, THF; $NaHCO_3$ aq./CH_2Cl_2 (see: J. Pitlik, G. Batta, F. Sztaricskai, *Liebigs Ann. Chem.* **1992**, 895−898) or NaH, THF) made no improvement. No identifiable side products (^1H, ^{13}C, ^{31}P NMR) were obtained and we suspect that irreversible deprotonation of **20** leads to decomposition of the enolate to give volatile products arising by fragmentation.

[24] Quenching the reaction with D_2O instead of H_2O had no effect on the deuterium incorporation. However, material balance indicated that the mol of **20** *not* converted into **22** tallied well with the amount of ^1H incorporation at C(3). Furthermore, there was no ^2H incorporation at C(1). This suggests that deprotonation of **20** is irreversible and that the liberated ^1H becomes redistributed by exchange of protons between the resulting the phosphonium salt and the ylide. See: H. J. Bestmann, *Chem. Ber.* **1962**, *95*, 58−63.

[25] M. Hesse, H. Meier, B. Zech, *Spectroscopic Methods in Organic Chemistry*, Stuttgart, Germany, **1997**.

[26] K. L. Bray, I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Commun.* **2001**, 187−188.

[27] K. L. Bray, I. J. S. Fairlamb, P. J. Kaiser, G. C. Lloyd-Jones, P. A. Slatford, unpublished results.

[28] [28a] J. Krause, G. Cestaric, K.-J. Haack, K. Seevogel, W. Storm, K.-R. Pörschke, *J. Am. Chem. Soc.* **1999**, *121*, 9807−9823.[28b] M. Gómez Andreu, A. Zapf, M. Beller, *Chem. Commun.* **2000**, in press.

[29] S. Hashiguchi, Y. Maeda, S. Kishimoto, M. Ochiai, *Heterocycles* **1986**, *24*, 2273−2283.

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