

Addition of Organolithium Reagents to Cinnamic Acids.

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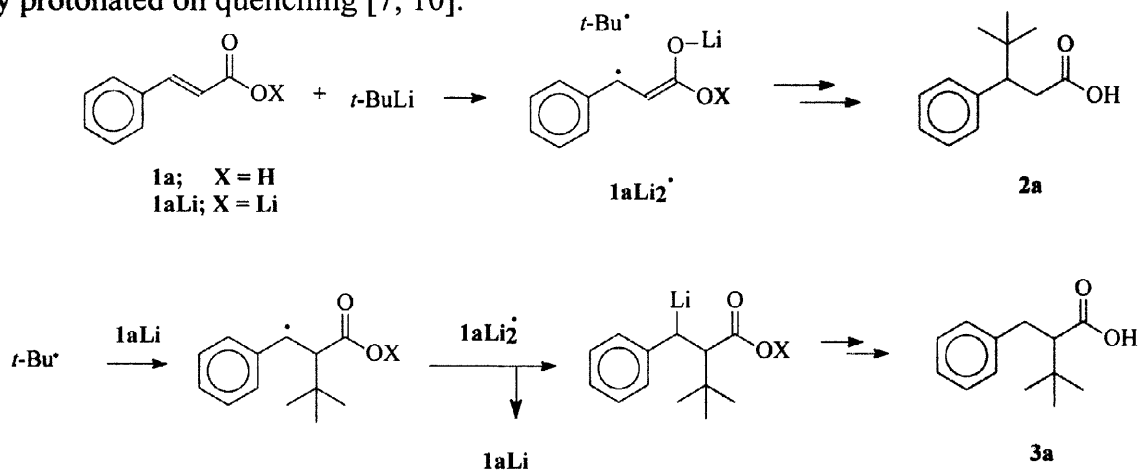
Abstract

Reaction of *tert*-butyllithium with *p*- and *m*-substituted cinnamic acids at low temperature affords mixtures of 1,4- and 1,3-addition products, whose composition depend on the nature of the substituents. Electron-donating and electron-withdrawing groups favour 1,4- and 1,3-additions, respectively. Linear correlations are obtained with electronic effect and with radical substituent constants. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Conjugate Addition; Unsaturated Carboxylic Acids; Organolithium

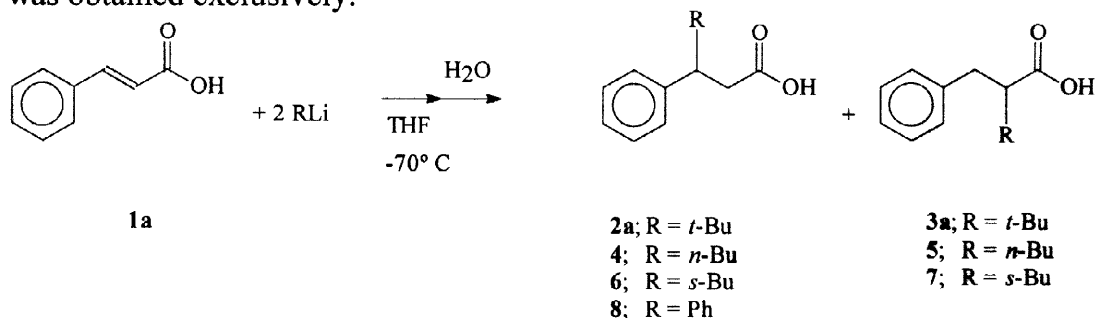
Organolithium reagents normally react with carboxylic acid lithium salts through nucleophilic addition to the carbonyl group to afford a dilithium α -dialkoxylate which on aqueous work-up enables isolation of a ketone [1-4]. The addition fails as a synthetic procedure for unsaturated carboxylic acids as substrates, when conjugate addition, double deprotonation and polymerisation compete with 1,2-addition [4,5]. We have shown that acrylic and unbranched alk-2-enoic acids undergo conjugated addition when allowed to react with alkyl and phenyl lithium reagents at low temperature to give conveniently 3-alkyl or 3-phenyl substituted carboxylic acids [6]. Similar additions of *n*- and *tert*-butyllithium to cinnamic acid had been carried out by Klummp, who reported a 60/40 mixture (64%) of Michael and *contra*-Michael adducts as the surprising result of the reaction of cinnamic acid with *tert*-butyllithium, and a 94/6 mixture (35% yield) obtained with *n*-butyllithium [7]. This competition between Michael and *contra*-Michael addition to cinnamic acid was preceded by the closely similar reaction of *tert*-butylmagnesium chloride with ethyl cinnamate in ether described by Crossland [8-10], who obtained a 60/40 mixture (70%) of the corresponding Michael and *contra*-Michael esters. Crossland and Klummp explained their findings by assuming (see Scheme 1 for addition of the alkyllithium reagent to cinnamic acid) that the 1,4-adduct was the result of a SET diffusionless radical coupling between *tert*-butyl radical and the dilithiated radical $1aLi_2^\bullet$,

whereas its 1,3-regioisomer derived from a chain radical mechanism, in which the diffused *tert*-butyl radical added to a molecule of the cinnamic lithium salt, the resulting benzyl radical would then be reduced by the lithiated radical $1aLi_2^\bullet$, and the resulting carbanion would be finally protonated on quenching [7, 10].



Scheme 1

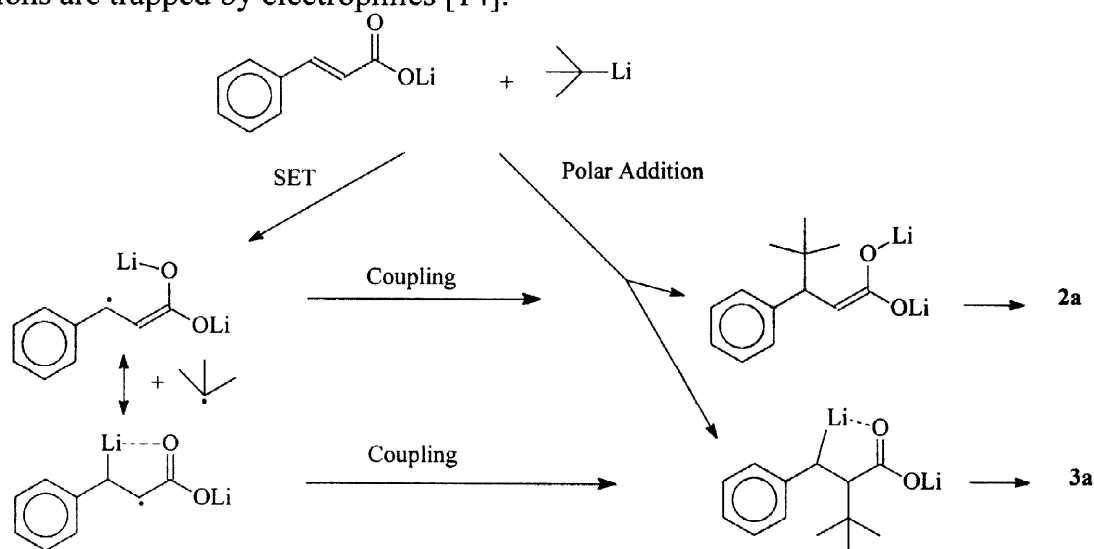
We now disclose our results on the addition of *tert*-butyllithium to cinnamic acids, which should contribute to a better understanding of this intriguing reaction. In our hands, reaction of *tert*- and *n*-butyllithium with cinnamic acid **1a** (Scheme 2) confirmed Klumpp's findings, except for the regioselectivity of the first addition, as we obtained a 37:63 (82%) mixture of Michael and *contra*-Michael adducts **2a** and **3a**. Similarly *n*-butyllithium led to the 1,4-adduct **4** (50% yield), though contaminated by a small amount of, probably, its 1,3-addition regioisomer **5** (1H NMR), which could not be removed from the mixture by distillation or by column chromatography. With *sec*-butyllithium cinnamic acid **1a** afforded diastereoisomeric mixtures of regioisomers **6** and **7** in a 60:40 ratio (GLC), separation of which was not attempted, and with phenyllithium the product of conjugate addition, 3,3-diphenylpropanoic acid **8** was obtained exclusively.



Scheme 2

Observation of both 1H and ^{13}C NMR spectra of the acid product mixture from addition of *tert*-butyllithium to cinnamic acid and to substituted cinnamic acids (see below) revealed no

significant acidic products other than those from 1,4- and 1,3-additions. The ^1H NMR spectra of the neutral fractions showed a complex mixture of saturated hydrocarbons, where no alkene protons were found, and aryl protons were hardly observed, thus showing that, under the conditions employed, 1,2-addition was negligible. These observations led us to postulate that competition between Michael and *contra*-Michael addition could be explained through a polar addition mechanism (Scheme 3), a SET-coupling mechanism, or a competition between both processes. Indeed, an ionic mechanism for *contra*-Michael addition is not entirely unlikely, and Beak advanced an ionic mechanism for this particular case, as an example of complex induced proximity effects (CIPE) [11-13]. Furthermore, Taylor has recently shown that organolithium reagents add to the double bond of styrene, and that the resulting benzylic carbanions are trapped by electrophiles [14].



Scheme 3

We were thus interested to find to what extent substituent effects would modify the regioselectivity of the reaction of *tert*-butyllithium with cinnamic acids. Additions of *tert*-butyllithium to a number of substituted cinnamic acids were thus carried out (Scheme 4). All reactions were run at the same concentrations of acceptors and reagents, by slow addition of the cinnamic acid in THF to the commercially available *tert*-butyllithium in pentane and THF at $-70\text{ }^\circ\text{C}$. In all cases the solution became instantly deep red; and the colour did not fade until quenching with water. *o*-Methoxycinnamic acid was exceptional in that a pink solution was observed instead. Acidic addition products were studied through the ^1H NMR spectra of the crude mixtures, and neutral products were not studied. Regioselectivity ratios, were determined from analysis of spectra of the mixtures after previous isolation of both regioisomers. This was very easily done thanks to the strong steric hindrance by the *tert*-butyl group on the Fischer esterification of the 1,3-adducts; the 1,4-adducts **2** were selectively esterified with refluxing

methanol and sulfuric acid, whereas the 1,3-adducts **3** remained substantially unchanged after 3 h under these conditions. The method enabled isolation and purification of the 1,4-adducts **2** as their methyl esters on the one hand, and of the 1,3-adducts **3** as free acids on the other. This easy resolution adds some synthetic interest to the present study, as it enables preparation, though not in high yields, of congested carboxylic acids.

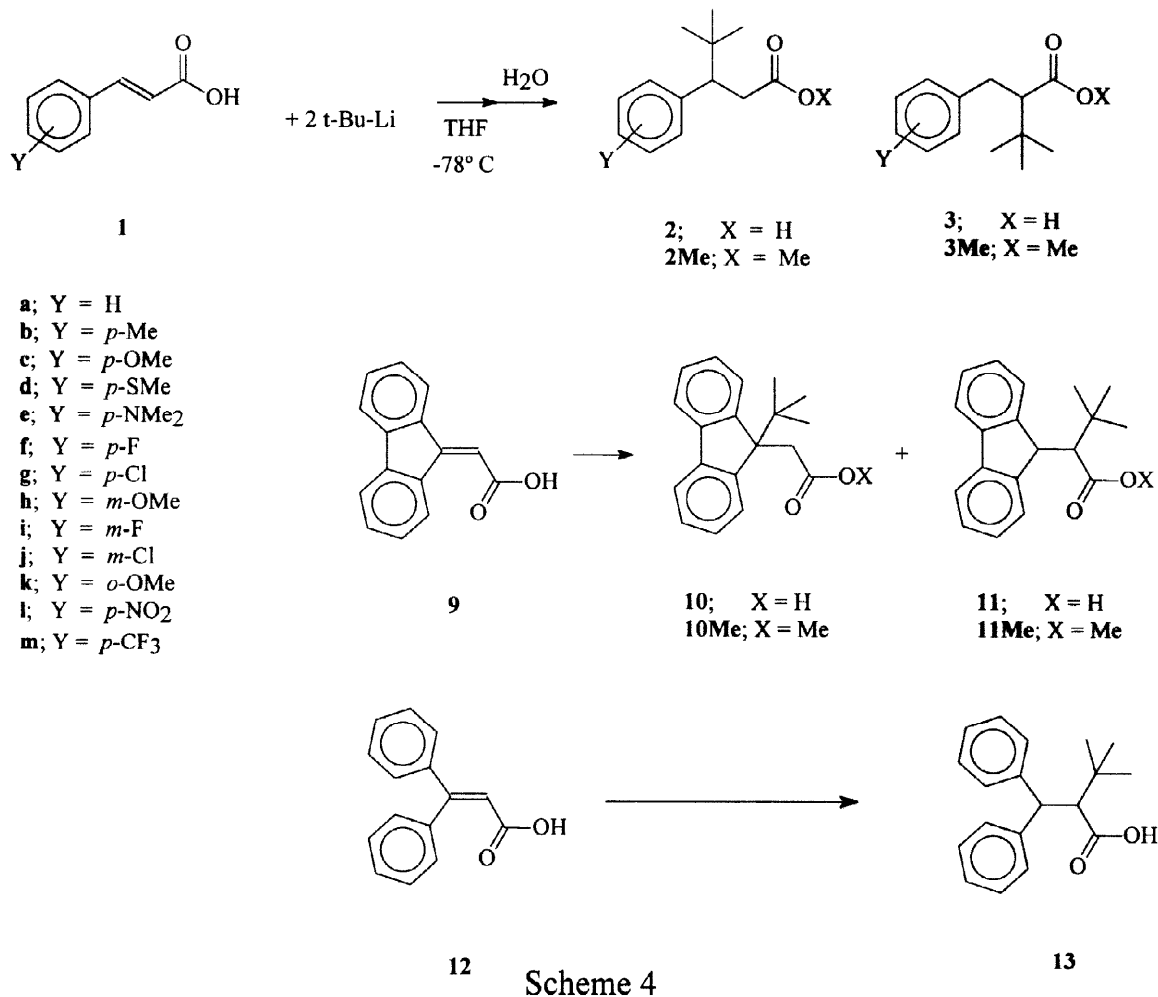


Table 1
Regioselectivity of addition of *tert*-butyllithium to cinnamic acids in THF at -78°C

Starting Acid	Yield (%)	1,4/1,3 ^a	Isolated adducts ^b (%)		Starting Acid	Yield (%)	1,4/1,3 ^a	Isolated adducts ^b (%)	
			2 ^c	3				2 ^c	3
1a	82	37 : 63	2a (30)	3b (37)	1h	84	36 : 64	2h (28)	3h (36)
1b	91	51 : 49	2b (32)	3b (32)	1i	88	31 : 69	2i (20)	3i (52)
1c	88	75 : 25	2c (50)	3c (11)	1j	84	21 : 79	2j (9)	3j (41)
1d	84	37 : 63	2d (18)	3d (44)	1k	88	42 : 58	2k (37)	3k (42)
1e	79	84 : 16	2e (38)	3e (8)	9	88	40 : 60	10 (29)	11 (34)
1f	90	54 : 46	2f (26)	3f (21)	12	73	< 1 : >99		13 (60)
1g	89	38 : 62	2g (11)	3g (21)					

a. Ratios obtained through ^1H NMR spectra of crude mixtures.

b. Spectroscopically and analytically pure compounds

c. Isolated as methyl esters

The direction of the addition is easily modified by steric effects. Indeed, when the organolithium reagent was added to the flat fluorenylideneacetic acid **9** (Scheme 4), substantially the same regioselectivity ratio was obtained as for cinnamic acid (Table 2), but 3,3-diphenylpropenoic acid **12**, with at least one the phenyl groups deviating from the plane of the rest of the conjugated system, led exclusively to the 1,3-addition product **13**.

The influence of electronic effects was examined when a number of *p*- and *m*-substituted cinnamic acids were used as acceptors (Scheme 4). Results for *p*-nitro and *p*-trifluoromethylcinnamic acids **11** and **1m** could not be obtained because of insolubility and polymerisation, respectively. Yields and regioselectivities obtained are shown in Table 1. It is easily observed that electron-withdrawing groups favour *contra*-Michael over Michael addition, whereas strong electron-donating groups lead to the opposite result. When the logarithms of the regioselectivity ratios were plotted *versus* substituent constants, the above substituent effect trends were confirmed, and linear correlations were obtained for σ constants ($R^2 = 0.8568$) and for Swain and Lupton's *R* and *F* constants ($R^2 = 0.8517$) (Figures 1 and 2) [17,18, 19]. There is not an obvious interpretation of the reaction constants obtained ($\rho = -1.02$ and -0.98 , respectively), as they are the difference between the ρ constants of 1,4- and 1,3-additions. As a consequence of the negative value of the combined ρ constants, it may be deduced that $\rho_{1,3}$ is more positive than $\rho_{1,4}$, and consequently a higher increase in electronic charge must develop in the transition state leading to 1,3-addition than in that leading to 1,4-addition. Thus, these correlations are in agreement with a ionic mechanism, but the radical anionic character of the SET intermediates would justify electronic affects as well. On the other hand, when the logarithms of the regiochemical ratios were plotted *versus* σ^- [20], a linear correlation ($R^2 = 0.8216$) was again obtained (Figure 3), thus showing that the substituent effects should be understood just as well through intermediacy of free radicals.

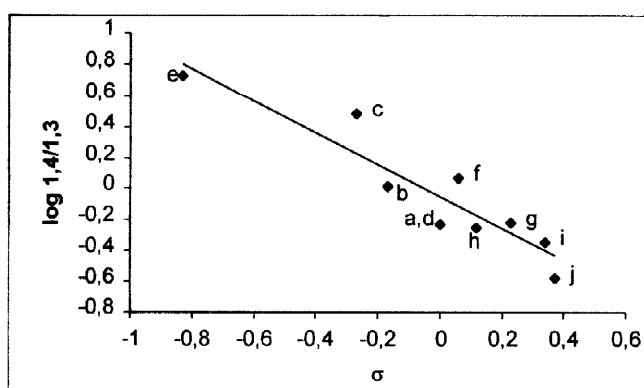


Figure 1

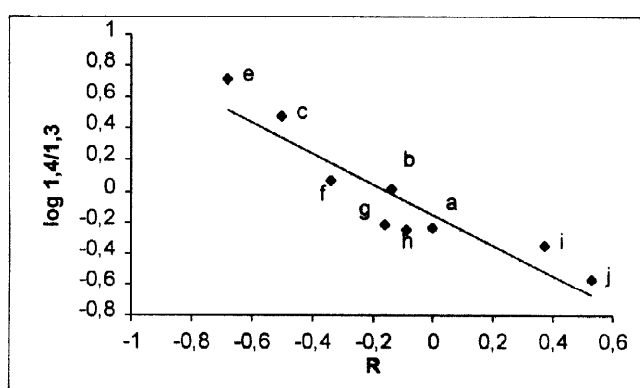


Figure 2

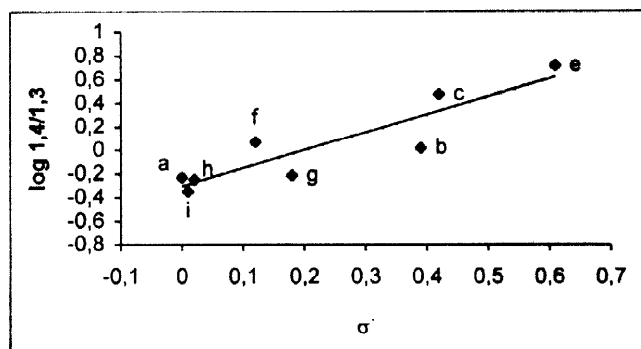
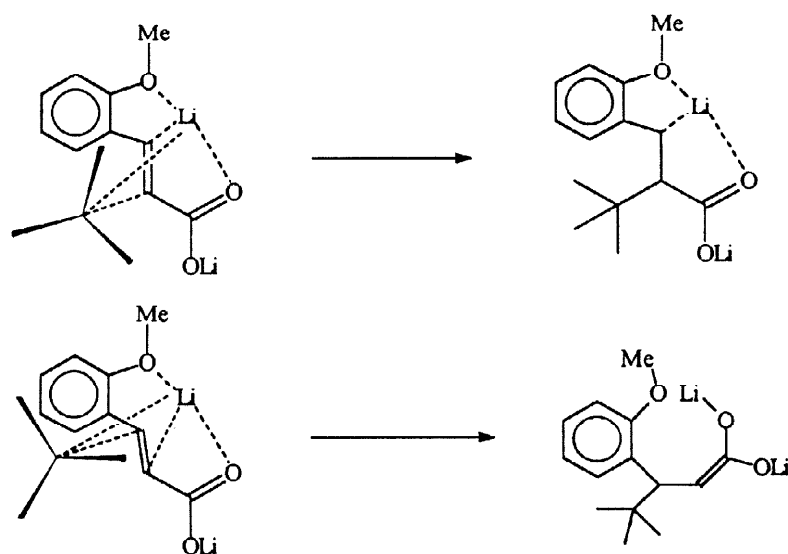


Figure 3

One further comment on substituent effects may be made when regioselectivities of the additions to *o*- and *p*-methoxycinnamic acids are compared. A shift from Michael to *contra*-Michael addition is found on going from *p*- to *o*-methoxy-cinnamic acids. Although steric hindrance might contribute, the difference is most probably due to the complexation of the lithium ion with the benzylic anionic carbon and with two oxygen atoms, which is possible on 1,3-addition to the *o*-methoxy- but not to the *p*-methoxy-cinnamic acid (Scheme 5).



Scheme 5

Crossland substantiated the above SET radical chain mechanism for addition of the *tert*-butyl Grignard reagent to ethyl cinnamate (Scheme 1) by the observation of the yield of the 1,3-adduct decreasing substantially in the presence of a radical scavenger, namely α -methylstyrene [10]. Further, *tert*-butyl radical generated from *tert*-butyldihydrobenzophenone gave almost

exclusively the 1,3-adduct on reaction with ethyl cinnamate and with cinnamic acid [10]. According to the same author, the Michael/*contra*-Michael regiochemical ratio is increased by use of excess of Grignard reagent (5:1), and decreased (1:1) when the reaction is carried out at higher concentrations (above 1 M).

Table 2
Addition of *tert*-butyllithium to cinnamic acid **1a**^a

Method ^{b,c}	Solvent (ml)		Radical trap (mmol)	Crude yield (%)	Unreacted Acid 1a (%)	1,4/1,3 2a:3a
	1a	<i>t</i> -BuLi				
A	20	10		82		37: 63
B	10	2.8		96		47: 53
A	5	8		70		49: 51
A ^d	20	100		70	20	39: 61
B	20	10	MS ^e (2.22)	84 ^f	< 5	43: 57
A	20	10	MS (5)	84 ^f	13	50: 50
A	20	10	DNB ^g (0.11)	- ^f		46: 54
B	20	10	DNB (0.6)	80 ^f	65	62: 38
A	20	10	DNB (2.22)	89 ^f	76	>81:<19

a. 2.25 mmol of cinnamic acid; 4.5 mmol of *tert*-butyllithium, THF -70 °C

b. Method A: Acid added slowly to the organometallic reagent at -70 °C

c. Method B: Organometallic reagent in hydrocarbon slowly added to the acid at -70 °C.

d. Mixture allowed to react for 4 h at -70 °C after addition of acid **1a**.

e. MS stands for α -methylstyrene, added along with cinnamic acid

f. Complex mixtures of acidic products (¹H NMR).

g. DNB stands for dinitrobenzene, added along with cinnamic acid

We also carried out a few experiments in order to find the influence of concentration, order of addition and presence of radical traps on the regioselectivity of the addition of *tert*-butyllithium to cinnamic acid **1a**, and the results obtained are given in Table 2. Not very significant regioselectivity changes were observed on modification of the order of addition of reagents or of their concentrations, when the reactions were carried out in the presence of radical traps, namely α -methylstyrene (MS) and *p*-dinitrobenzene (DNB) [10, 15, 16]. Not surprisingly, starting cinnamic acid **1a** was partly recovered, and much more complex mixtures were obtained (¹H NMR). However, what is more important, these radical traps caused a significant decrease in the relative amount of 1,3-adduct **3a**, as the spectra of the crude mixtures revealed, thus showing that MS, and especially DNB, interfere with the process which leads to the 1,3-adduct. Although from the present experiments it is not possible to tell whether the Michael addition is interfered with as well, a radical mechanism seems likely for the *contra*-Michael addition.

In conclusion, we have shown that steric and electronic effects modify the regioselectivity of the addition of *tert*-butyllithium to cinnamic acids: *contra*-Michael addition predominates

except in the presence of strong electron-donating groups, which favour Michael addition. Although these effects can be explained through competing ionic additions, significant relative decrease of 1,3-adduct in the presence of radical traps is indicative of a SET process. Separate values of the electronic substituent effect constants for 1,4- and 1,3-additions, as well as cyclicvoltametric studies will be required for a clear distinction between polar and radical mechanisms, or for evaluation of the contribution of each pathway to the results of these additions to cinnamic acids. On the other hand, a well defined experimental distinction between a SET-coupling mechanism and the SET radical chain process as that described by Crossland will need to surmount the added complication of the aggregation state in which lithium carboxylates are present in solution.

Experimental

IR Spectroscopic data were obtained for liquid films or KBr discs with a Perkin-Elmer 281 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded for CDCl_3 solutions, unless otherwise stated, with Bruker AC-200 (200 MHz) or 300 Varian Unity (300 MHz) spectrometers, using TMS as internal standard. Mass spectra were determined with VG Autospec or Trio 1000 spectrometers; EI and CI stand for electronic impact and chemical ionization, respectively. Melting points were measured with a Reichert apparatus and are uncorrected. Silica gel Merck 60 (0.06–0.20 mm) was used for column chromatography, and silica gel Merck 60 (230–400 mesh) for flash column chromatography; elution was with hexane/ether mixtures, unless otherwise stated. Tetrahydrofuran (THF) was distilled from blue sodium diphenylketyl immediately before use. All reactions were carried out under argon atmosphere, using standard conditions for exclusion of moisture. The reaction temperature ($-70\text{ }^\circ\text{C}$) was achieved by cooling with a CO_2 /acetone bath. Evaporation of solvents was carried out with a vacuum rotatory evaporator at $40\text{ }^\circ\text{C}$. Organolithium reagents and most cinnamic acids were purchased from Aldrich. *p*-Methylthiocinnamic acid **1d**, 3-(9-fluorenylidene)propenoic acid **10** and 3,3-diphenylpropenoic acid **12** were prepared by conventional methods.

General procedure for addition of organometallic reagents to cinnamic acids.

The cinnamic acid (2.25 mmol) in THF (20 ml) was added slowly to the organolithium reagent (4.5 to 5 mmol) in a stirred hydrocarbon/THF solution (10 ml) at $-70\text{ }^\circ\text{C}$. The solution was stirred for 1 h at the same temperature. Water (30 ml) was added, and the mixture extracted with ether ($3 \times 15\text{ ml}$). The aqueous layer was acidified, under stirring and ice-water cooling, by slow addition of conc hydrochloric acid and then extracted with ethyl acetate ($4 \times$

15 ml). The joint organic layers were dried. Evaporation of the solvent gave a mixture of adducts. The composition of this mixture was determined through its ^1H NMR spectrum.

Mixtures of *tert*-butyl adducts were resolved by selective esterification according to the general procedure which follows.

General procedure for isolation of *tert*-butyl adducts. The crude mixture of adducts was heated for 3 h under reflux in methanol (15 ml) and conc sulfuric acid (5 ml). The solution was extracted with hexane (4×10 ml). The upper layer was washed twice with 1 N sodium hydroxide and once with brine and dried. Evaporation of the solvent gave the corresponding crude methyl ester of acid **2**, which was purified by column chromatography on silica gel (hexane:ether 97:3).

The alkaline aqueous layer was acidified with conc hydrochloric acid, saturated with ammonium chloride and extracted with ethyl acetate (4×10 ml). The organic layer was washed with brine and dried. Evaporation of the solvent gave the corresponding acid **3**, frequently spectroscopically pure. When needed, this product was purified by column chromatography on silica gel (hexane:ether 9:1).

3,3-Diphenylpropanoic acid 8. Cinnamic acid (0.33 g; 2.25 mmol) and phenyllithium (3.6 ml; 1.8 M; 6.5 mmol) were allowed to react according to the general procedure to give yellow prisms of the title acid (0.29 g; 57%), mp 148–150 °C (lit [151] mp 154.5–155.5 °C); δ_{H} 7.22 (10 H, m, Ar-H), 4.51 (1 H, t, J 7.9 Hz, C3-H) and 3.08 (2 H, d, J 7.9 Hz, C2); δ_{C} 178.3 (C=O), 143.3 (ArC), 128.6 (ArCH), 127.6 (ArCH), 126.7 (ArCH), 46.6 (C2) and 40.5 (C3).

Addition of *tert*-butyllithium to cinnamic acid 1a. According to the general method, cinnamic acid (0.333 g; 2.25 mmol) and *tert*-butyllithium (2.8 ml; 1.7 M; 4.5 mmol) gave a 63:37 mixture of 4,4-dimethyl-3-phenylpentanoic and 2-phenylmethyl-3,3-dimethylbutanoic acids **2a** and **3a** (0.379 g; 82%). The mixture was esterified with methanol according to the general procedure. From the organic layer, methyl 4,4-dimethyl-3-phenylpentanoate **2aMe** was obtained as a colourless oil (0.147 g; 30%); δ_{H} 7.22 (5 H, m, Ar-H), 3.74 (3 H, s, CH₃O), 3.00 (1 H, dd, J 5.0 and 10.6 Hz, C3-H), 2.74 (2 H, m, C2-H) and 0.90 (9 H, s, $3 \times \text{CH}_3$); δ_{C} 173.5 (C=O), 139.1 (ArC), 129.2 (ArCH), 127.5 (ArCH), 126.2 (ArCH), 52.1 (CH₃O), 51.4 (C3), 35.5 (C2 and C4) and 27.9 ($3 \times \text{CH}_3$) [21].

3,3-Dimethyl-2-phenylmethylbutanoic acid **3a** was isolated from the alkaline aqueous layer as colourless prisms (0.17 g; 37%), mp 69–71 °C. ν_{max} 3200–2450 (OH) and 1680 (C=O) cm^{-1} ; δ_{H} 7.18 (5 H, m, Ar-H), 2.84 (2 H, m, CH₂), 2.44 (1 H, dd, J 6.2, 8.7 Hz, C2-H) and 1.01 (9 H, s, $3 \times \text{CH}_3$); δ_{C} 180.9 (C=O), 139.9 (ArC), 128.6 (ArCH), 128.4 (ArCH), 126.2 (ArCH), 58.6 (C2), 33.8 (CH₂), 32.9 (C3) and 27.8 ($3 \times \text{CH}_3$) [7, 22].

Addition of *tert*-butyllithium to *p*-methylcinnamic acid 1b. According to the general procedures, *p*-methylcinnamic acid **1b** (0.365 g; 2.25 mmol) and *tert*-butyllithium (2.8 ml; 1.7 M; 4.7 mmol) gave a 49:51 mixture of adducts **2b** and **3b** (0.452 g; 91%). From the organic layer, **methyl 4,4-dimethyl-3-(4-methylphenyl)pentanoate 2bMe** was obtained as colourless prisms (0.170 g; 32%); mp 32–34 °C. Found: (EI) M^+ 234.1620. $C_{15}H_{22}O_2$ requires 234.1618. ν_{\max} 1735 (C=O) cm^{-1} ; δ_H 7.05 (4 H, s, Ar-H), 3.47 (3 H, s, CH₃O), 2.95 (1 H, dd, J 5.1 and 10.5 Hz, C3-H), 2.74 (2 H, m, C2-H), 2.30 (3 H, s, Ar-CH₃) and 0.88 (9 H, s, 3 × CH₃); δ_C (APT) 173.6 (C=O), 138.4 (ArC), 135.7 (ArC), 129.1 (ArCH), 128.3 (ArCH), 51.7 (CH₃O), 51.4 (C3), 35.5 (C2) and 33.6 (C4), 27.9 (3 × CH₃) and 21.0 (Ar-CH₃).

From the aqueous layer **3,3-dimethyl-2-[(4-methylphenyl)methyl]butanoic acid 3b** was obtained as colourless prisms (0.156 g; 32%); mp 131–132 °C. Found: (EI) M^+ 220.1463. $C_{14}H_{20}O_2$ requires 220.1463. ν_{\max} 3400–2500 (OH) and 1690 (C=O) cm^{-1} ; δ_H 7.05 (4 H, s, Ar-H), 2.82 (2 H, m, CH₂), 2.43 (1 H, dd J 5.3 and 9.8 Hz, C2-H), 2.31 (3 H, s, Ar-CH₃) and 1.07 (9 H, s, 3 × CH₃); δ_C 180.6 (C=O), 136.8 (ArC), 135.6 (ArC), 129.1 (ArCH), 128.5 (ArCH), 58.7 (C2), 33.4 (Ar-CH₂), 32.9 (C3), 27.8 (3 × CH₃) and 21.0 (Ar-CH₃).

Addition of *tert*-butyllithium to *p*-methoxycinnamic acid 1c. *p*-Methoxycinnamic acid **1c** (0.401 g) and *tert*-butyllithium as usual gave a 75:25 mixture of adducts **2c** and **3c** (0.465 g; 88%), which was esterified according to the general procedure. From the organic layer **methyl 4,4-dimethyl-3-(4-methoxyphenyl)pentanoate 2cMe** was obtained as colourless prisms (0.284 g; 50%), mp 35–57 °C. Found: (CI) M^+ 250.1569 $C_{15}H_{22}O_3$ requires 250.1568. ν_{\max} 1730 (C=O) cm^{-1} ; δ_H 7.06 (2 H, d, J 8.7 Hz, ArC2-H), 6.80 (2 H, d, J 8.7 Hz, ArC3-H), 3.78 (3 H, s, CH₃O-Ar), 3.47 (3 H, s, CH₃O), 2.87 (1 H, dd, J 4.5 and 11.1 Hz, C3-H), 2.74 (2 H, m, C2-H) and 0.86 (9 H, s, 3 × CH₃); δ_C (APT) 173.7 (C=O), 158.0 (ArC4), 133.6 (ArC1), 130.1 (ArC2), 113.3 (ArC3), 55.1 (Ar-OCH₃), 51.6 and 51.5 (CH₃O and C3), 35.6 (C2), 33.7 (C4) and 27.8 (3 × CH₃).

From the aqueous layer **3,3-dimethyl-2-(4-methoxyphenylmethyl)butanoic acid 3c** was obtained as colourless prisms (0.115 g; 11%), mp 56–57 °C (lit[22] mp 54–56 °C). Found: (CI) M^+ 236.1412 $C_{14}H_{20}O_3$ requires 236.1413. ν_{\max} 3500–2400 (OH), and 1670 (C=O) cm^{-1} ; δ_H 7.07 (2 H, d, J 6.8 Hz, C2-H), 6.79 (2 H, d, J 6.8 Hz, C3-H), 3.77 (3 H, s, CH₃O), 2.80 (2 H, m, Ar-CH₂), 2.41 (1 H, dd, J 5.3 and 9.8 Hz, C2-H), and 1.07 (9 H, s, 3 × CH₃); δ_C (APT) 180.7 (C=O), 158.0 (ArC4), 131.9 (ArC1), 129.6 (ArC2), 113.8 (ArC3), 58.9 (C2), 55.1 (CH₃O), 32.9 (Ar-CH₂ and C3) and 27.9 (3 × CH₃) [22].

Addition of *tert*-butyllithium to *p*-methylthiocinnamic acid 1d. *p*-Methylthiocinnamic acid **1d** (0.437 g) and *tert*-butyllithium gave a 37:63 mixture of adducts **2d** and **3d**, respectively (0.477 g; 84%) as a yellow solid material. Esterification and purification

according to the general procedure gave **methyl 4,4-dimethyl-3-(4-methylthiophenyl)pentanoate 2dMe** as yellow prisms (0.109 g; 18%), mp 75–77 °C. Found: (CI) M^+ 266.1341. $C_{15}H_{22}O_2S$ requires 266.1342. ν_{\max} 1700 (C=O) cm^{-1} ; δ_H 7.15 (2 H, d, J 8.6 Hz, ArC3-H), 7.08 (2 H, d, J 8.6 Hz, ArC2-H), 3.47 (3 H, s, CH₃O), 2.94 (1 H, dd, J 5.01 and 11.0 Hz, C3-H), 2.73 (2 H, m, C2-H), 2.46 (3 H, s, CH₃-S) and 0.87 (9 H, s, 3 × CH₃); δ_C (APT) 173.4 (C=O), 138.5 (ArC1), 135.9 (ArC4), 129.7 (ArC2), 126.0 (ArC3), 51.7 (CH₃O), 51.4 (C3), 35.4 (C2), 33.7 (C4), 27.8 (3 × CH₃) and 15.8 (CH₃-S).

From the aqueous layer **3,3-dimethyl-2-(4-methylthiophenylmethyl)butanoic acid 3d** was isolated as colourless prisms (0.250 g; 44%), mp 110–113 °C. Found: (CI) M^+ 252.1184 $C_{14}H_{20}O_2S$ requires 252.1180. ν_{\max} 3100–2500 (OH), and 1670 (C=O) cm^{-1} ; δ_H 7.15 (2 H, d, J 8.3 Hz, ArC3-H), 7.08 (2 H, d, J 8.3 Hz, ArC2-H), 2.82 (2 H, m, CH₂), 2.44 (1 H, m, C2-H), 2.43 (3 H, s, CH₃-S) and 1.07 (9 H, s, 3 × CH₃); δ_C (APT) 180.7 (C=O), 136.9 (ArC1), 135.9 (ArC4), 129.2 (ArC2), 127.0 (ArC3), 58.6 (C2), 33.3 (Ar-CH₂), 33.0 (C3), 27.8 (3 × CH₃) and 16.0 (CH₃-S).

Addition of *tert*-butyllithium to *p*-dimethylaminocinnamic acid 1e. *p*-Dimethylaminocinnamic acid **1e** (0.430 g) and *tert*-butyllithium were allowed to react as usual. The reaction mixture was diluted with water, the solvent partly evaporated and the mixture extracted with ethyl ether, as described in the general procedure. The aqueous layer was acidified to pH 4 and extracted with ethyl acetate (4 × 15 ml) and with dichloromethane (3 × 15 ml). Evaporation of the combined extracts gave a 16:84 mixture of adducts **2e** and **3e** (0.465 g; 79%;) as a red solid material, which was esterified according to the general procedure. The reaction mixture was made alkaline with sodium hydroxide (1 M) and extracted with ethyl acetate (4 × 10 ml) and with dichloromethane (3 × 10 ml). Evaporation of solvents and purification allowed isolation of **methyl 4,4-dimethyl-3-(4-dimethylaminophenyl)pentanoate 2eMe** as yellow prisms (0.224 g; 38%), mp 57–60 °C. Found: (EI) M^+ 263.1885 $C_{16}H_{25}O_2N$ requires 263.1882. ν_{\max} 1710 (C=O) cm^{-1} ; δ_H 7.02 (2 H, d, J 8.7 Hz, ArC2-H), 6.64 (2 H, d, J 8.7 Hz, ArC3-H), 3.48 (3 H, s, CH₃O), 2.91 (6 H, s, 2 × CH₃-N), 2.87 (1 H, m, C3-H), 2.72 (2 H, m, C2-H) and 0.87 (9 H, s, 3 × CH₃); δ_C (APT) 173.8 (C=O), 149.1 (ArC4), 129.8 (ArC2), 129.5 (ArC1), 111.9 (ArC3), 51.4 and 51.3 (CH₃O and C3), 40.6 (2 × CH₃-N), 35.6 (C2), 33.9 (C4) and 27.9 (3 × CH₃).

The aqueous alkaline layer was acidified with hydrochloric to pH 4 and extracted with ethyl acetate (4 × 10 ml) and with dichloromethane (3 × 10 ml). Evaporation of the solvent and purification of the residue by column chromatography on silica gel (hexane: ethyl acetate 85:15) gave **2-(4-dimethylaminophenylmethyl)-3,3-dimethylethyl-butanoic acid 3e** as colourless prisms (0.044 g; 8%), mp 170–172 °C. Found: (EI) M^+ 249.1729 $C_{15}H_{23}O_2N$ requires

249.1728. ν_{\max} 3150–2500 (OH), and 1680 (C=O) cm^{-1} ; δ_{H} 7.04 (2 H, d, J 8.7 Hz, ArC2-H), 6.68 (2 H, d, J 8.7 Hz, ArC3-H), 2.88 (6 H, s, $2 \times \text{CH}_3\text{-N}$), 2.77 (2 H, m, CH_2), 2.41 (1 H, dd, J 4.8 and 10.2 Hz, C2-H), and 1.06 (9 H, s, $3 \times \text{CH}_3$); δ_{C} (APT) 180.2 (C=O), 149.0 (ArC4), 129.3 (ArC2), 128.7 (ArC1), 113.5 (ArC3), 58.7 (C2), 41.1 ($2 \times \text{CH}_3\text{N}$), 32.8 (CH_2 and C3) and 27.9 ($3 \times \text{CH}_3$).

Addition of *tert*-butyllithium to *p*-fluorocinnamic acid 1f. From *p*-fluorocinnamic acid **1f** (0.374 g) and *tert*-butyllithium, a 46:54 mixture of adducts **2f** and **3f** (0.456 g; 91%) was obtained. Separation of the mixture by esterification as above led to **methyl 4,4-dimethyl-3-(4-fluorophenyl)pentanoate 2fMe** as a colourless oil (0.124 g; 26%). Found: (EI) M^+ 238.1369. $\text{C}_{14}\text{H}_{19}\text{O}_2\text{F}$ requires 238.1373. ν_{\max} 1735 (C=O) cm^{-1} ; δ_{H} 7.12 (2 H, dd, J 4.4 and 7.7 Hz, ArC2-H), 6.4 (2 H, t, J 8.7 Hz, ArC3-H), 3.47 (3 H, s, CH_3O), 2.97 (1 H, dd, J 4.7 and 11.3 Hz, C3-H), 2.72 (2 H, m, C2-H) and 0.87 (9 H, s, $3 \times \text{CH}_3$); δ_{C} (APT) 173.4 (C=O), 161.5 (d, J 242.9 Hz, ArC4), 137.1 (ArC1), 130.6 (ArC2), 114.4 (d, J 21.1 Hz, ArC3), 51.5 (C3 and CH_3O), 35.5 (C2), 33.6 (C4) and 27.8 ($3 \times \text{CH}_3$).

From the aqueous layer, after purification, **3,3-dimethyl-2-(4-fluorophenylmethyl)-butanoic acid 3f** was obtained as colourless prisms (0.097 g; 21%); mp 41–43 °C. Found: (EI) M^+ 224.1213. $\text{C}_{13}\text{H}_{17}\text{O}_2\text{F}$ requires 224.1213. ν_{\max} 3400–2500 (OH) and 1700 (C=O) cm^{-1} ; δ_{H} 7.10 (2 H, dd, J 5.7 and 8.4 Hz, ArC2-H), 6.93 (2 H, t, J 8.4 Hz, ArC3-H), 2.81 (2 H, m, CH_2), 2.41 (1 H, dd, J 6.6 and 8.7 Hz, C2-H), and 1.06 (9 H, s, $3 \times \text{CH}_3$); δ_{C} (APT) 180.1 (C=O), 161.5 (d, J 2.42 Hz, ArC4), 135.4 (d, J, 3.5 Hz, ArC1), 130.1 (d, J 7.5 Hz, ArC2), 115.2 (d, J 21.1 Hz, ArC3), 58.7 (C2), 32.9 (CH_2 and C3) and 27.8 ($3 \times \text{CH}_3$).

Addition of *tert*-butyllithium to *p*-chlorocinnamic acid 1g. Under the usual conditions *p*-chlorocinnamic acid **1g** (0.411 g) and *tert*-butyllithium led to a 62:38 mixture of adducts **2g** and **3g** (0.391 g; 72%). Selective esterification allowed isolation of **methyl 3-(4-chlorophenyl)-4,4-dimethylpentanoate 2gMe** as a colourless oil (0.114 g; 11%). Found: (CI) $\text{M}^{(37)\text{Cl}}^+$ 256.1044 and $\text{M}^{(35)\text{Cl}}^+$ 254.1074. $\text{C}_{14}\text{H}_{19}\text{O}_2\text{Cl}$ requires 256.1132 and 254.1135. ν_{\max} 1730 (C=O) cm^{-1} ; δ_{H} 7.23 (2 H, d, J 6.7 Hz, ArC3-H), 7.09 (2 H, d, J 6.7 Hz, ArC2-H), 3.48 (3 H, s, CH_3O), 2.96 (1 H, dd, J 4.5 and 11.1 Hz, C3-H), 2.73 (2 H, m, C2-H) and 0.87 (9 H, s, $3 \times \text{CH}_3$); δ_{C} (APT) 173.3 (C=O), 140.0 (ArC1), 132.1 (ArC4), 130.5 (ArC2), 128.4 (ArC3), 51.6 and 51.5 (CH_3O and C3), 35.5 (C2), 33.6 (C4) and 27.8 ($3 \times \text{CH}_3$).

From the aqueous layer, **2-(4-chlorophenylmethyl)-3,3-dimethylbutanoic acid 3g** was obtained as colourless prisms (0.115 g; 21%), mp 52–53 °C. Found: (CI) $\text{M}^{(37)\text{Cl}}^+$ 242.0888 and $\text{M}^{(35)\text{Cl}}^+$ 240.0917. $\text{C}_{13}\text{H}_{17}\text{O}_2\text{Cl}$ requires 242.0916 and 240.0914. ν_{\max} 3300–2700 (OH) and 1690 (C=O) cm^{-1} ; δ_{H} 7.22 (2 H, d, J 6.6 Hz, ArC3-H), 7.08 (2 H, d, J 6.6 Hz, ArC2-H), 2.82 (2 H, m, CH_2), 2.42 (1 H, dd, J 5.9 and 9.2 Hz, C2-H), and 1.05 (9 H, s, $3 \times \text{CH}_3$); δ_{C} (APT) 179.6

(C=O), 138.3(ArC1), 132.1 (ArC4), 130.0 (ArC2), 128.5 (ArC3), 58.4 (C2), 33.1(Ar-CH₂), 33.0 (C3) and 27.8 (3 × CH₃) [23].

Addition of *tert*-butyllithium to *m*-methoxycinnamic acid 1h. *m*-Methoxycinnamic acid **1h** (0.401 g) and *tert*-butyllithium as usual led to a 64:36 mixture of adducts **2h** and **3h** (0.472 g; 89%). Selective esterification as above allowed isolation of **methyl 4,4-dimethyl-3-(3-methoxyphenyl)pentanoate 2hMe** as a colourless oil (0.155 g; 28%). Found: (CI) M⁺ 250.1569. C₁₅H₂₂O₃ requires 256.1575. ν_{\max} 1720 (C=O) cm⁻¹; δ_{H} 7.17 (1 H, t, J 8.1 Hz, Ar-H), 6.74 (3 H, m, 3 × Ar-H), 3.79 (3 H, s, Ar-OCH₃), 3.49 (3 H, s, CH₃O), 2.96 (1 H, dd, J 5.1 and 10.2 Hz, C3-H), 2.73 (2 H, m, C2-H) and 0.89 (9 H, s, 3 × CH₃); δ_{C} (APT) 173.5 (C=O), 158.9 (ArC3), 143.3 (ArC1), 128.4 (ArC5), 121.8 (ArC6), 115.5 (ArC2), 111.2 (ArC4), 55.1 (ArOCH₃), 52.1 (CH₃O), 51.5 (C3), 35.5 (C2), 33.6 (C4) and 28.0 (3 × CH₃).

From the aqueous layer **3,3-dimethyl-2-(3-methoxyphenylmethyl)butanoic acid 3h** was obtained as colourless prisms (0.155 g; 36%), mp 58-60 °C. Found: (CI): (M+)⁺ 237.1491. C₁₄H₂₀O₃ requires 237.1486. ν_{\max} 3300-2500 (O-H) and 1700 (C=O) cm⁻¹; δ_{H} 7.17 (1 H, t, J 7.7 Hz, Ar-H), 6.75 (3 H, m, 3 × Ar-H), 3.75 (3 H, s, CH₃O), 2.86 (2 H, m, Ar-CH₂), 2.47 (1 H, dd, J 4.5 and 10.5 Hz, C2-H) and 1.08 (9 H, s, 3 × CH₃); δ_{C} (APT) 18.9 (C=O), 159.6 (ArC3), 141.5 (ArC1), 129.4 (ArC5), 121.0 (ArC6), 114.2 (ArC2), 111.8 (ArC4), 58.5 (C2), 55.0 (Ar-OCH₃), 33.9 (CH₂), 33.0 (C3) and 27.8 (3 × CH₃).

Addition of *tert*-butyllithium to *m*-fluorocinnamic acid 1i. According to the general method, *m*-fluorocinnamic acid **1i** (0.437 g; 2.25 mmol) and *tert*-butyllithium (2.8 ml; 1.7 M) gave a mixture of adducts (0.447 g; 88%; 69:31) which was esterified as above to give after purification **methyl 4,4-dimethyl-3-(3-fluorophenyl)pentanoate 2iMe** as a colourless oil (0.048 g; 20%). Found: M⁺ (EI) 238.1369 C₁₄H₁₉O₂F requires 238.1367. ν_{\max} 1700 (C=O) cm⁻¹; δ_{H} 7.21 (1 H, m, Ar-H), 6.90 (3 H, m, 3×Ar-H), 3.48 (3 H, s, CH₃O), 2.99 (1 H, dd, J 4.5 and 10.8 Hz, C3-H), 2.73 (2 H, m, C2-H) and 0.89 (9 H, s, 3 × CH₃); δ_{C} (APT) 173.2 (C=O), 162.3 (d, J 243.3 Hz, ArC3), 144.3 (d, J 7.0 Hz, ArC1), 128.9 (d, J 8.6 Hz, ArC5), 125.0 (ArC6), 116.0 (d, J 20.0 Hz, ArC2), 113.2 (d, J 21.1 Hz, ArC4), 51.9 (CH₃O), 51.5 (C3), 35.4 (C2), 33.6 (C4) and 27.9 (3 × CH₃).

From the aqueous layer **3,3-dimethyl-2-(3-fluorophenylmethyl)butanoic acid 3i** was obtained as yellow prisms (0.262 g; 52%), mp 50-53 °C. Found: M⁺ (EI) 224.1213 C₁₃H₁₇O₂F requires 224.1214. ν_{\max} 3250-2500 (OH), and 1690 (C=O) cm⁻¹; δ_{H} 7.22 (1 H, m, Ar-H), 6.89 (3 H, m, 3 × Ar-H), 2.86 (2 H, m, CH₂), 2.44 (1 H, dd, J 5.1 and 10.2 Hz, C2-H) and 1.07 (9 H, s, 3 × CH₃); δ_{C} (APT) 179.9 (C=O), 162.8 (d, J 243.8 Hz, ArC3), 142.4 (d, J, 7.0 Hz, ArC1), 129.8 (d, J 8.0 Hz, ArC5), 124.3 (d, J 3 Hz, ArC6), 115.6 (d, J, 21.1 Hz, ArC2), 113.2 (d, J 21.0 Hz, ArC4), 58.3 (C2), 33.6 (CH₂), 33.0 (C3) and 27.8 (3 × CH₃).

Addition of *tert*-butyllithium to *m*-chlorocinnamic acid 1j. *m*-Chlorocinnamic acid **1j** (0.437 g; 2.25 mmol) and *tert*-butyllithium similarly led to a mixture of adducts (0.457 g; 84%; 79:21) which was esterified with methanol. From the organic layer **methyl 3-(3-chlorophenyl)-4,4-dimethylpentanoate 2jMe** was obtained as a colourless oil (0.050 g; 9%). Found: (CI) $M(^{37}\text{Cl})^+$ 256.1044 and $M(^{35}\text{Cl})^+$ 254.1074 $\text{C}_{14}\text{H}_{19}\text{O}_2\text{Cl}$ requires 256.1108 and 254.1077. ν_{max} 1730 (C=O) cm^{-1} ; δ_{H} 7.18 (3 H, m, 3 \times Ar-H), 7.04 (1 H, m, Ar-H), 3.47 (3 H, s, CH_3O), 2.94 (1 H, dd, J 4.7 and 11.0 Hz, C3-H), 2.71 (2 H, m, C2-H) and 0.86 (9 H, s, 3 \times CH_3); δ_{C} (APT) 173.2 (C=O), 143.8 (ArC1), 133.5 (ArC3), 129.6 (ArCH), 128.9 (ArCH), 126.6 (2 \times ArCH), 51.9 (CH_3O), 51.6 (C3), 35.3 (C2), 33.7 (C4) and 27.8 (3 \times CH_3).

From the aqueous layer and after purification **2-(3-chlorophenylmethyl)-3,3-dimethylbutanoic acid 3j** was obtained as colourless prisms (0.22 g; 41%), mp 41–43 °C. Found: (CI) $M(^{37}\text{Cl})^+$ 242.0888 and $M(^{35}\text{Cl})^+$ 240.0917 $\text{C}_{13}\text{H}_{17}\text{O}_2\text{Cl}$ requires 242.0927 and 240.0914. ν_{max} 3400–2500 (OH), and 1700 (C=O) cm^{-1} ; δ_{H} 7.17 (3 H, m, 3 \times Ar-H), 7.05 (1 H, m, Ar-H), 2.85 (2 H, m, CH_2), 2.45 (1 H, dd, J 4.7 and 10.4 Hz, C2-H) and 1.08 (9 H, s, 3 \times CH_3); δ_{C} (APT) 180.6 (C=O), 142.0 (ArC1), 134.1 (ArC3), 129.7 (ArCH), 128.9 (ArCH), 126.9 (ArCH), 126.5 (ArCH), 58.4 (C2), 33.5 (CH_2), 33.0 (C3) and 27.8 (3 \times CH_3).

Addition of *tert*-butyllithium to *o*-methoxycinnamic acid 1h. *o*-Methoxycinnamic acid **1k** (0.401 g) and *tert*-butyllithium were allowed to react as usual to give a 58:42 mixture of adducts **2k** and **3k** (0.465 g; 88%) as a yellow oil, which was esterified according to the general procedure. From the organic layer an oil was obtained, which was purified to give **methyl 4,4-dimethyl-3-(2-methoxyphenyl)pentanoate 2kMe** as a colourless oil (0.207 g; 37%). Found: (CI) M^+ 250.1569. $\text{C}_{15}\text{H}_{22}\text{O}_3$ requires 256.1561. ν_{max} 1740 (C=O) cm^{-1} ; δ_{H} 7.13 (2 H, m, Ar-H), 6.87 (2 H, m, Ar-H), 3.82 (3 H, s, Ar-OCH₃), 3.79 (1 H, m, C3-H), 3.46 (3 H, s, CH_3O), 2.74 (2 H, m, C2-H) and 0.88 (9 H, s, 3 \times CH_3); δ_{C} (APT) 173.6 (C=O), 158.0 (ArC2), 127.9 (ArC6), 127.0 (ArC4), 125.5 (ArC1), 119.8 (ArC5), 110.7 (ArC3), 55.6 (Ar-OCH₃), 51.3 (CH_3O), 41.1 (C3), 35.4 (C2), 34.2 (C4) and 27.5 (3 \times CH_3).

Extraction of the aqueous layer and purification gave **3,3-dimethyl-2-(2-methoxyphenylmethyl)butanoic acid 3k** as colourless prisms (0.222 g; 42%), mp 152–153 °C. Found: (EI) M^+ 236.,1412. $\text{C}_{14}\text{H}_{20}\text{O}_3$ requires 236.1409. ν_{max} 3150–2400 (O-H) and 1680 (C=O) cm^{-1} ; δ_{H} 7.19 (1 H, d, J 1.5 and 7.8 Hz, ArC4-H), 7.10 (1 H, dd, J 1.5 and 7.5 Hz, ArC6-H), 6.82 (2 H, m, 2 \times Ar-H), 3.01 (1 H, dd, J 2.4 and 13.2 Hz, Ar-CH₂), 2.75 (1 H, dd, J 11.4 and 13.2 Hz, Ar-CH₂), 2.51 (1 H, dd, J 2.4 and 11.4 Hz, C2-H) and 1.09 (9 H, s, 3 \times CH_3); δ_{C} (APT) 181.4 (C=O), 157.5 (ArC2), 130.2 (ArC6), 128.4 (ArC1), 127.6 (ArC4), 120.4 (ArC5), 110.1 (ArC3), 56.2 (C2), 55.0 (Ar-OCH₃), 33.1 (C3) 29.0 (Ar-CH₂) and 27.7 (3 \times CH_3).

Addition of *tert*-butyllithium to 9-fluorenylideneacetic acid 9. 9-Fluorenylideneacetic acid **9** (0.500 g; 2.25 mmol) and *tert*-butyllithium (2.8 ml; 1.7 M) gave a 60:40 mixture of adducts **10** and **11** (0.557; 88%) as yellow solid material. Selective esterification and purification of the material obtained from the organic layer allowed isolation of 9-(1,1-dimethylethyl)-9-(methoxycarbonylmethyl)fluorene **10Me** as colourless prisms (0.191 g; 29%), mp 55–57 °C. Found: (EI) M^+ 294.1620. $C_{20}H_{22}O_2$ requires 294.1629. ν_{\max} 1735 (C=O) cm^{-1} ; δ_H 7.70 (2 H, dd, J 0.9 and 7.5 Hz, 2 × Ar-H), 7.49 (2 H, dd, J 0.3 and 7.5 Hz, 2 × Ar-H), 7.35 (2 H, dt, J 1.2 and 7.5 Hz, 2 × Ar-H), 7.26 (2 H, dt, J 1.2 and 7.5 Hz, 2 × Ar-H), 3.29 (3 H, s, CH₃O), 3.09 (2 H, s, CH₂) and 0.92 (9 H, s, 3 × CH₃); δ_C (APT) 171.2 (C=O), 148.2 (ArC), 141.8 (ArC), 127.1 (ArCH), 125.9 (ArCH), 125.1 (ArCH), 119.4 (ArCH), 58.4 (C9), 51.0 (CH₃O), 37.3 (C-CH₃), 37.2 (CH₂) and 26.4 (3 × CH₃) [24].

From the aqueous layer and after purification **2-(9-fluorenyl)-3,3-dimethylbutanoic acid 11** was obtained as colourless prisms (0.217 g; 34%), mp 185–186 °C. Found: (EI) M^+ 280.1463. $C_{19}H_{18}O_2$ requires 280.1461. ν_{\max} 3150–2400 (O-H), 1700 (C=O) cm^{-1} ; δ_H 7.73 (1 H, t, J 7.7 Hz, Ar-H), 7.62 (1 H, d, J 7.5 Hz, Ar-H), 7.50 (1 H, d, J 7.8 Hz, Ar-H), 7.38 (1 H, t, J 6.8 Hz, Ar-H), 7.31 (2 H, m, 2 × Ar-H), 7.23 (1 H, dt, J 1.2 and 7.5 Hz, 2 × Ar-H), 4.14 (1 H, s, C9-H), 3.15 (1 H, s, CH-CO₂H), and 1.12 (9 H, s, 3 × CH₃); δ_C (APT) 177.2 (C=O), 147.0 (ArC), 144.6 (ArC), 141.2 (ArC), 140.9 (ArC), 127.2 (ArCH), 127.1 (ArCH), 126.6 (ArCH), 125.7 (ArCH), 124.9 (ArCH), 119.6 (ArCH), 57.7 (CH-CO₂H), 46.5 (C9), 33.4 (C-CH₃) and 28.8 (3 × CH₃).

2-Diphenylmethyl-3,3-dimethylbutanoic acid 13. 3,3-Diphenylpropenoic acid **12** (0.504 g; 2.25 mmol) was allowed to react with *tert*-butyllithium (2.8 ml; 1.7 M), affording a single compound (0.464 g; 73%), which crystallized from hexane-ether to give colourless crystals of **2-diphenylmethyl-3,3-dimethylbutanoic acid 13** (0.379 g; 60%), mp 186–188 °C. Found: (EI) M^+ 282.1620 $C_{19}H_{22}O_2$ requires 282.1617. ν_{\max} 3150–2500 (O-H), and 1690 (C=O) cm^{-1} ; δ_H 7.26 (10 H, m, 10 × Ar-H), 4.24 (1 H, d, J 11.9 Hz, CH-Ar), 3.31 (1 H, d, J 11.9 Hz, C2-H) and 0.83 (9 H, s, 3 × CH₃); δ_C (APT) 179.5 (C=O), 144.0 (ArC), 143.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.6 (ArCH), 126.5 (ArCH), 126.4 (ArCH), 59.2 (C2), 51.9 (Ar-CH), 33.5 (C3) and 29.0 (3 × CH₃).

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