Conjugate Addition of Organolithium Reagents to α,β-Unsaturated Carboxylic Acids.

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Abstract

Conjugate addition of primary, secondary, tertiary alkyl and phenyl lithium reagents to 2-alkenoic acids affords good yields of branched saturated carboxylic acids. Methyl groups at the α- and β-carbon of the 2-alkenoic acid decrease reactivity as acceptors, and foster deprotonation, respectively. The lithium enediolate resulting from the conjugate addition can react with electrophiles. PM3 calculations are in agreement with the substituent effects. © 1998 Published by Elsevier Science Ltd. All rights reserved.

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Conjugate additions of carbon centred nucleophilic reagents to the C-C double bonds of unsaturated aldehydes, ketones, esters and amides, are of utmost importance in synthetic methodology [1]. Grignard reagents usually lead to mixtures of 1,2- and 1,4-addition products, whose ratios are strongly dependent on the structure of the acceptor. Thus, unsaturated aldehydes undergo exclusively 1,2-addition, conjugate addition predominates for unsaturated amides, whereas steric effects apparently control the regioselectivity of the addition of organomagnesium reagents to unsaturated ketones [2]. 1,2-Addition products are usually obtained on reaction of organolithium reagents with unsaturated aldehydes, ketones and esters [3]. However, it has been established for long time that conjugate addition of organomagnesium reagents to unsaturated ketones and esters can be attained by catalytic amounts of copper (I) salts [1, 4, 5], and organocuprates are presently acknowledged as the reagents of choice for these conjugate additions [2, 4, 6]. In spite of the latter generalization, the possibility of attaining 1,4-additions of organolithium reagents would certainly mean an important simplification in synthetic methodology, as organocuprates usually require previous

generation of those reagents. A number of authors have obtained predominant conjugate addition of organolithium reagents by prevention of 1,2-addition through steric congestion around the carbonyl group. This is the case for tritylenones, *N,N,N*-trimethylacrylhydrazides, some *N,N*-disubstituted acrylamides, or acrylic esters of 2,6-di-*tert*-butylphenols [3, 7]. The success of conjugate additions to unsaturated chiral oxazolines and amides as acceptors has provided methods for asymmetric syntheses of carboxylic acid derivatives [8-13]. In a different approach, charge directed 1,4-addition occurs when the carbonyl group is conjugated to an anionic carbon or nitrogen atom. This has been observed for acrylic *N*-monosubstituted amides [14] or for acrylmethylenetriphenylphosporanes [3]. Charge directed conjugate addition of organomagnesium and organolithium reagents has also been described for α-silylated unsaturated carboxylic acids. The α-silyl group favours here the conjugate addition and prevents polymerisation, an undesirable side process frequently found in additions of organolithium or organomagnesium to acrylic systems [15].

Addition of organolithium reagents to carboxylic acids is usually acknowledged as a general procedure for the synthesis of ketones [16-19]. Ambient or higher temperatures are usually required and the resulting ketones are frequently accompanied by the alcohols whenever the organometallic reagent is still present when the reaction mixture is quenched [16, 18]. However, poor yields of ketones are usually reported for α,β-unsaturated carboxylic acids, and products resulting from double deprotonation of the starting carboxylic acid and small amounts of conjugate addition acids result [16, 20]. On the other hand, poor selectivities usually result for conjugate addition of organomagnesium reagents to unsaturated carboxylic acids [21, 22]. Although organocuprates fail, primary alkyl organocuprous-boron trifluoride complexes afford 1,4-addition products on reaction with unsaturated carboxylic acids [23, 24]. Some scattered 1,4-additions of organolithium reagents to unsaturated carboxylic acids have been reported. This is the case for the addition of organolithium reagents to naphthoic acids as acceptors [25], or the additions to cinnamic acid [26]. However, as far as we know, the synthetic applicability and scope of the conjugate addition of organolithium to unsaturated carboxylic acids has not been thoroughly studied. On account of the results obtained for other acceptors, a charge directed conjugate addition to unsaturated carboxylic acids is to be expected, provided deprotonation of the carboxylic group occurs more rapidly than 1,2-addition, an assumption which has been shown to be true at low temperature [27].

We wish to describe here in full our own findings on the conjugate addition of organolithium reagents to simple 1,2-unsaturated carboxylic acids, namely acrylic and butenoic acids or higher homologues, and to show that this addition may stand as a convenient synthetic method within limitations determined mainly by the presence and site of alkyl substituents at the alkene double bond. Experimental findings here described are in agreement

with semiempirical PM3 calculations. A preliminary account of part of this study has already been published [28]. The study of the peculiarities of a similar addition to cinnamic acids is described in the accompanying publication.

We have used throughout this work commercially available organolithium reagents purchased as their hydrocarbon or hydrocarbon/ether solutions. As described in the Experimental, a solution of the unsaturated carboxylic acid in THF has been usually added to 2.2 equivalents of the organolithium reagent in a mixture of the hydrocarbon solvent and THF at -70 °C. Solutions have been allowed to react for 1 or 2 h at the same temperature, although a few experiments showed that the reactions had come to their end much sooner. These standard conditions have been occasionally modified by performing inverse addition, namely addition of the solution of the organolithium reagent as commercially available to the THF solution of the acid at -70 °C, or by increasing reaction time or/and temperature. Acid fractions of the reaction mixtures have been studied through their ^{1}H and ^{13}C NMR spectra, and particular addition products have been isolated only when estimated yields showed the addition to be synthetically useful. Neutral fractions are constituted by small amounts of complex mixtures which have not been further studied.

1; R^1 = H
2; R^1 = Me

3; R^1 = H
4; R^1 = Me

a; R = *n*-Bu
b; R = *sec*-Bu
c; R = *tert*-Bu
d; R = Ph
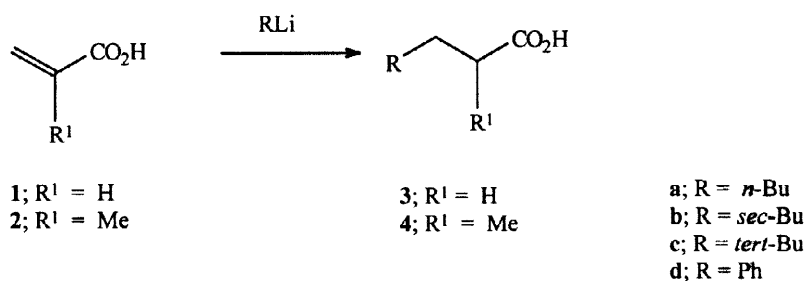
Scheme 1

Table 1

Addition or organolithium reagents to acrylic acids.

Entry	Starting acid	R	Method [a]	Product (%) [b, c]
1	1	*n*-Bu	A	3a (43)
2	1	*tert*-Bu	B	3c (42)
3	1	*tert*-Bu [d]	A	3c (58)
4	1	Ph	A	3d (32)
5	2	*n*-Bu	A	4a (26)
6	2	*tert*-Bu	A	4c (74)
7	2	Ph	A	4d (12)

a. Method A: Addition of the starting acid to stirred RLi. Method B: Addition of RLi to stirred starting acid
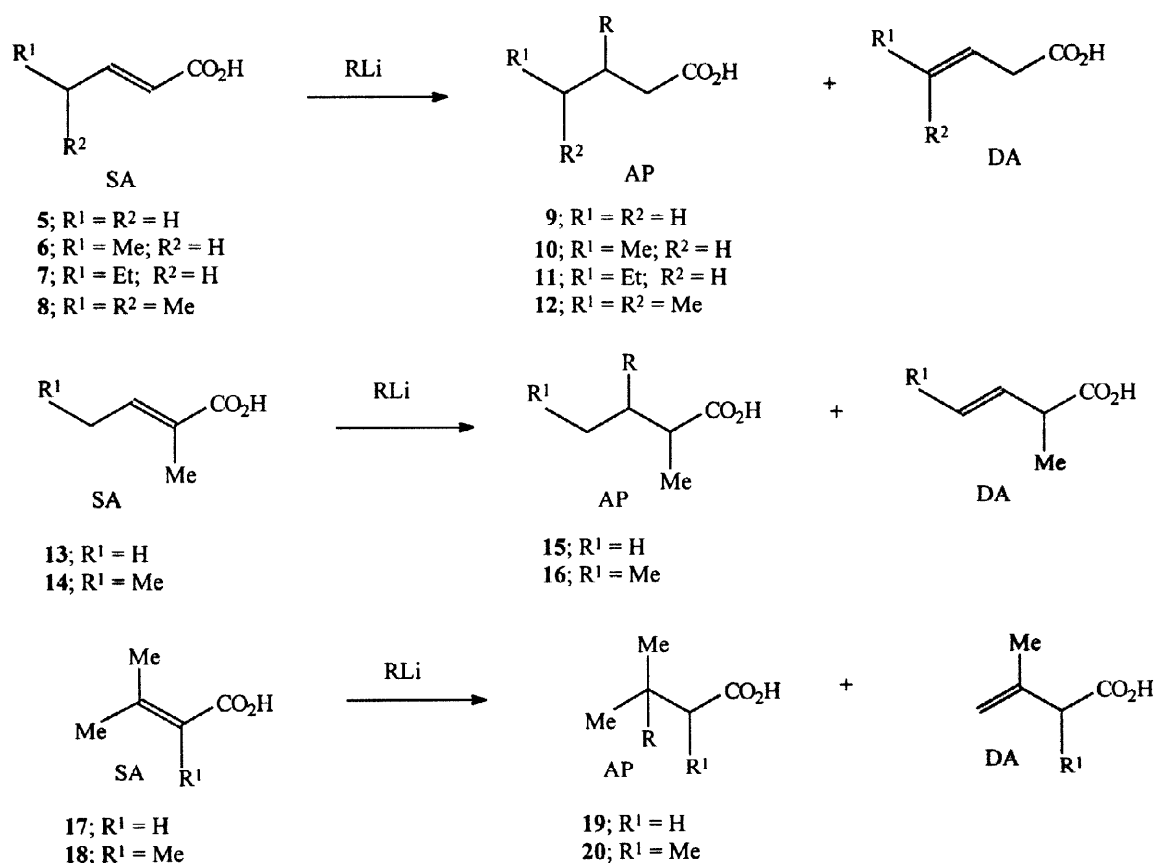
b. Purified by bulb-to-bulb distillation.

c. Chromatographically (GLC) and spectroscopically (^{1}H and ^{13}C NMR) pure samples obtained.

d. Carried out under more diluted conditions; see experimental

For acrylic acids 1,4- and 1,2-additions are frequently accompanied by polymerisation. Thus, addition of *n*-butyl-, *tert*-butyl- and phenyl-lithium to acrylic acid **1** and methacrylic acid **2** afford high amounts of crude materials, but only moderate yields of the acids derived from conjugate addition by bulb-to-bulb distillation (Scheme 1 and Table 1). However, yields can be improved on dilution of reagents, as has been found for the reaction of *tert*-butyllithium and acrylic acid **1** (entry 3). Satisfactory addition has also been obtained with *tert*-butyllithium and methacrylic acid **2** (entry 6).

For but-2-enoic acids and higher homologues, deprotonation at C-4 may compete with the additions (Scheme 2 and Table 2). This deprotonation leads to dienediolates which are protonated at C-2 on quenching [29], and thus acid fractions of the reaction mixtures may be expected to be constituted by the unreacted starting acid (SA), the addition product (AP), and the deconjugated isomer of the starting acid (DA). Other side reactions are feasible, namely Michael additions of the 1,4-addition enolates to unreacted unsaturated carboxylic acid lithium salt [30], but starting and deconjugated acids are the most significant side components of the reaction mixtures.

5; $R^1 = R^2 = H$
6; $R^1 = Me; R^2 = H$
7; $R^1 = Et; R^2 = H$
8; $R^1 = R^2 = Me$

9; $R^1 = R^2 = H$
10; $R^1 = Me; R^2 = H$
11; $R^1 = Et; R^2 = H$
12; $R^1 = R^2 = Me$

13; $R^1 = H$
14; $R^1 = Me$

15; $R^1 = H$
16; $R^1 = Me$

17; $R^1 = H$
18; $R^1 = Me$

19; $R^1 = H$
20; $R^1 = Me$

Scheme 2

Table 2

Addition or organolithium reagents to α,β-unsaturated carboxylic acids.

Entry	SA	R	Method [a]	Reaction Time (h)	Crude yield(%) [c]	SA:DA:AP [b]	AP [b](%) [d,e]
1	5	Me	A	1	100 [f]	100: 0: 0	
2		n-Bu	A	1	75	0: 0:100	12b (65)
3			B	2	66	50: 0: 50	
4		sec-Bu	A	0.5	75	0:<1: 99	12c (63) [g]
5			A	1	74	0:<1: 99	
6		tert-Bu	A	1	76	0:18: 82	
7			B	2	82	0: 9: 91	12d (69)
8		Ph	A	0.5	67	38: 0: 62	
9			A	1	93	0: 0:100	12e (77)
10			B	2	64	59: 0: 41	
11	6	n-Bu	A	1	68	<1: 0: 99	13b (55)
12		sec-Bu	A	1	69	0: 0:100	13c (56)
13		tert-Bu	B	0.5	76	0: 0:100	13d (67)
14		Ph	A	1	79	30: 0: 70	13e (60)
15	7	sec-Bu	A	1	60	15:11: 74	14c (44) [g]
16		tert-Bu	A	1	75	20:10: 70	14d (59)
17	8	n-Bu	A	1	47	53:<1: 47	15b (22)
18		tert-Bu	A	1	54	67:<1: 33	
19			A	2.5 (-30 °C)	55	72: 6: 22	
20			B	0.5	56	42: 0: 58	15d (23)
21			B	2.5	63	50: 0: 50	15d (22)
22	13	tert-Bu	A	1	59	59:23: 18	
23			B	2	56	54:27: 19	
24		Ph	A	1	61	61:<1: 39	
25			A	5 (-30 °C)	69	45: 5: 50	16e (43)
26	14	n-Bu	A	1	45	70: 0: 30	
27		tert-Bu	B	0.5	63	[h]	
28	17	n-Bu	A	1	66 [f]	37: 63: 0	
29		tert-Bu	A	1	79 [f]	28: 72: 0	
30			B	2	94 [f]	12: 88: 0	
31		Ph	A	1	87 [f]	55: 45: 0	
32	18	tert-Bu	A	1	48	55:45: 0	

a. Method A: Addition of the starting acid to stirred RLi. Method B: Addition of RLi to stirred starting acid.

b. SA: starting acid, DA: deconjugated acid, AP: addition product (see Scheme 2).

c. Calculated for 1,4-addition product.

d. Purified by bulb-to-bulb distillation.

e. Chromatographically (GLC), spectroscopically (^{1}H and ^{13}C NMR) and analytically pure samples obtained.

f. Yield estimated for SA and/or DA as product.
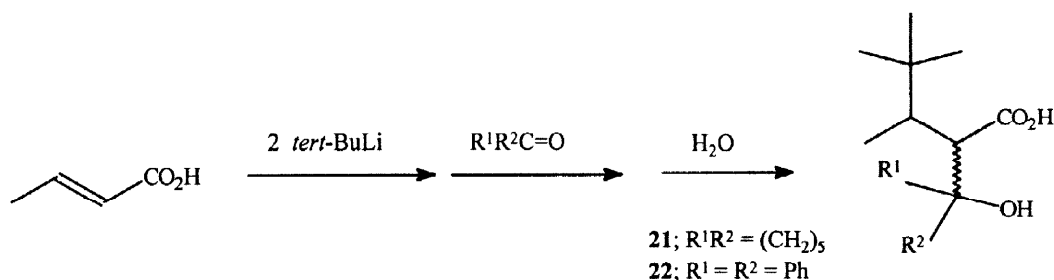
g. Isolated as a diastereoisomeric mixture.

h. Relative amounts not established.

Moderate to good yields for pure conjugate addition acids can be obtained for unsubstituted 2-alkenoic acids on addition of either primary, secondary or tertiary butyllithium reagents or of phenyllithium. However, for the longer chain hex-2-enoic acid 7 deprotonation competes with addition (entries 15 and 16). Steric congestion may hinder the addition, as is observed for the branched chain 4-methylpent-2-enoic acid 8 which adds n- and tert-butyllithium with difficulty

(entries 17-21); side reaction products are observed, although the deconjugated acid is not found, and isolation of addition products from the crude mixtures is not as simple as for the unbranched 2-alkenoic acids 5-7. A methyl group at the α-carbon of the unsaturated carboxylic acid atom renders conjugate addition sluggish and large amounts of unreacted 2-methylbut-2-enoic and 2-methylpent-2-enoic acids 13 and 14 are recovered (entries 22-26). Deprotonation becomes the predominant process when a methyl group is present as a branch at the β-ethylenic carbon, as is found for 3-methyl- and 2,3-dimethyl-buten-2-oic acids 17 and 18; no conjugate addition products are observed then in the acid fractions, and the corresponding deconjugated acids are obtained in good yields (entries 28-32).

Of the organolithium reagents, best yields for additions to unbranched 2-alkenoic acids are obtained with *tert*-butyllithium and phenyllithium. Addition of the acid to the solution of the organometallic reagent (Method A) affords better yields than addition of the organolithium reagent to a solution of the acid (Method B). Surprisingly methyllithium, either dissolved in pentane or in ether fails to afford any of the expected conversions on but-2-enoic acid 5.

Under non-protic conditions, conjugate additions lead to enolates, which may be trapped by an electrophile. When reactions of *tert*-butyllithium with but-2-enoic acid 5 were followed by addition of cyclohexanone and benzophenone, highly congested hydroxy acids 21 and 22 were obtained (Scheme 3).

$$\text{CO}_2\text{H} \quad \xrightarrow{2\ \textit{tert}\text{-BuLi}} \quad \xrightarrow{R^1R^2C=O} \quad \xrightarrow{H_2O} \quad$$

21; $R^1R^2 = (CH_2)_5$
22; $R^1 = R^2 = Ph$

Scheme 3

The two main limitations found in the additions of organolithium reagents to unsaturated carboxylic acids, namely alkyl branching at either α or β carbon atoms, are not uncommon. Yields for conjugate additions to α-alkyl substituted alkenoic acid derivatives are generally lower than for the unsubstituted compounds, as has been observed for addition of organocopper reagents to 2-methylbut-2-enoic acid 13 [24] and for addition of organolithium reagents to related unsaturated compounds [31]. On the other hand, Weiler showed that LDA deprotonates 3-methylbutenoic acid and its methyl ester selectively at the methyl group *cis* to the carboxyl or methoxycarbonyl group [32, 33].

We wanted to complete the present study finding out whether PM3 semiempirical calculations could account for the sluggish conjugate addition and the facile deprotonation due to the presence of a methyl group at α and β carbon atoms, respectively. This study has been done for reaction of *tert*-butyllithium with but-2-enoic, 2-methylbut-2-enoic, and 3-methylbut-2-enoic acids **5, 13** and **17**.

It has been assumed that *tert*-butyllithium reacts firstly with the acidic carboxylic hydrogen of these acids to afford the corresponding lithium salts, being the lithium atom co-ordinated to both carboxylic oxygen atoms. In a previous theoretical study devoted to the structure of lithium dienediolates of these acids in solution, we reported on the necessity of solvatation of the lithium atoms with ether solvent molecules to make up a tetra-co-ordination sphere of the metal, in order to obtain a correct description of these species in solution [34, 35]. In consequence, the lithium atoms have been co-ordinated now with dimethyl ether solvent molecules.

For each acid two pathways have been considered. Pathway A correspond to E-γ-hydrogen abstraction to give the metallation products, while the pathway B correspond to the 1,4-nucleophilic addition of the *tert*-butyllithium reagent. For 3-methylbut-2-enoic acid **17**, a third pathway C must be considered, namely Z-γ-metallation.

The carboxylic salt and the *tert*-butyllithium initially form a molecular complex (MC), where the lithium atom of the organolithium reagent is co-ordinated to one of the oxygen atoms of the carboxylate group, and to one ether molecule.[1] These MCs, **MC-I, MC-II** and **MC-III** (**I, II**, and **III** correspond with the **5, 13** and **17** acids, respectively), have then been used as precursor structures along the competing reaction pathways A, B and C. Metallation and nucleophilic addition activation energies for the elementary steps have been calculated relative to these MCs, in gas phase and with solvent effects (PM3 and PM3-solvent effects).

PM3 heats of formation and activation energies in gas phase and with solvent effects are reported in Table 3. Inclusion of solvent effects decreases significantly the energy of all species (11-15 kcal mol^{-1}) giving lower activation energies; these values are in better agreement with experimental results and, consequently, they will be used throughout the discussion.

A study of the potential energy surface for these reacctions, allow us to find three transition structures (TSs), corresponding to the three reaction pathway considered, **TS1-X** (pathway A), **TS2-X** (pathway B), and **TS3-III** (pathway C) (X=I, II and III). Table 4 show selected geometrical parameters for the different TSs, while Figure 1 and 2 present theirs geometries.

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[1] Although this complex accepts initially two ether molecules, one of them is expelled in approaching the TS, probably due to steric congestion associated with the bulk of the *tert*-butyl group.

Table 3.

PM3 Heats of Formation and Activation Energies in kcal mol^{-1}.

		PM3		PM3-solvent effects	
		ΔH_f	AE	ΔH_f	AE
But-2-enoic acid 5					
complex		-275.2		-288.3	
addition	**TS1-I**	-253.2	22.0	-267.7	20.6
metallation	**TS2-I**	-253.6	21.6	-267.4	20.9
2-Methylbut-2-enoic acid 13					
complex		-281.4		-293.5	
addition	**TS1-II**	-258.4	23.0	-271.7	21.8
metallation	**TS2-II**	-259.6	21.8	-272.9	20.7
3-Methylbut-2-enoic acid 17					
complex		-283.3		-295.1	
addition	**TS1-III**	-250.6	32.7	-265.1	30.0
metallation	**TS2-III**	-258.7	24.6	-272.8	22.3
metallation	**TS3-III**	-271.0	12.3	-282.4	12.7

Table 4.

Selected geometrical parameters for transition structures obtained with PM3 calculations (in parenthesis) and PM3- solvent effects. [a]

	TS1-I	TS1-II	TS1-III		TS2-I	TS2-II	TS2-III	TS3-III
C4-C6	2.326	2.313	2.319	**C6-H8**	1.629	1.620	1.598	1.586
	(2.271)	(2.269)	(2.262)		(1.601)	(1.597)	(1.574)	(1.581)
C3-C4	1.388	1.397	1.399	**C5-H8**	1.282	1.290	1.304	1.351
	(1.390)	(1.399)	(1.401)		(1.315)	(1.319)	(1.336)	(1.359)
C2-C3	1.440	1.447	1.435	**C3-C4**	1.359	1.364	1.365	
	(1.436)	(1.445)	(1.431)		(1.362)	(1.367)	(1.368)	(1.359)
O1-Li7	1.925	1.913	1.923	**O1-Li7**	2.055	2.046	2.059	1.969
	(1.907)	(1.901)	(1.903)		(2.049)	(2.042)	(2.057)	(1.958)
C6-Li7	2.345	2.341	2.440	**C6-Li7**	2.551	2.569	2.621	2.390
	(2.363)	(2.355)	(2.470)		(2.537)	(2.539)	(2.589)	(2.381)
C3-Li7	2.837	2.893	2.868	**C3-Li7**	2.718	2.796	2.617	2.867
	(2.800)	(2.860)	(2.834)		(2.661)	(2.741)	(2.556)	(2.866)
C3-C4-C5	117.4	119.2	115.5	**C4-C5-H9**	116.7	115.2	116.1	113.0
	(117.0)	(118.8)	(115.2)		(116.8)	(115.4)	(116.2)	(112.8)
O1-C2-C3-C4	12.8	13.4	17.2	**O1-C2-C3-C4**	47.1	44.4	60.2	49.5
	(14.0)	(14.6)	(18.1)		(48.8)	(44.7)	(62.2)	(49.7)

(a) Bond lengths in Å and bond and dihedral angles in degrees.

Along the nucleophilic attack of the *tert*-butyllithium to the C4 atom of the carboxylic salts (pathway A), the lithium atom is being co-ordinated to the C3 atom, but still maintaining its co-ordination with the oxygen atom of the carboxylate group (see Figure 1).

At **TS1-I**, the length of the C4-C6 forming bond is 2.326 Å, whereas the C3-C4 bond length stretches up to 1.388 Å, a feature indicative of the conversion of a double to a single bond. Similarly, the value of the C3-C4-C5 bond angle (117.4°) shows a sp^2 to sp^3 rehybridization of the C4 centre. An activation energy of 20.6 kcal mol^{-1} is calculated for this nucleophilic attack.
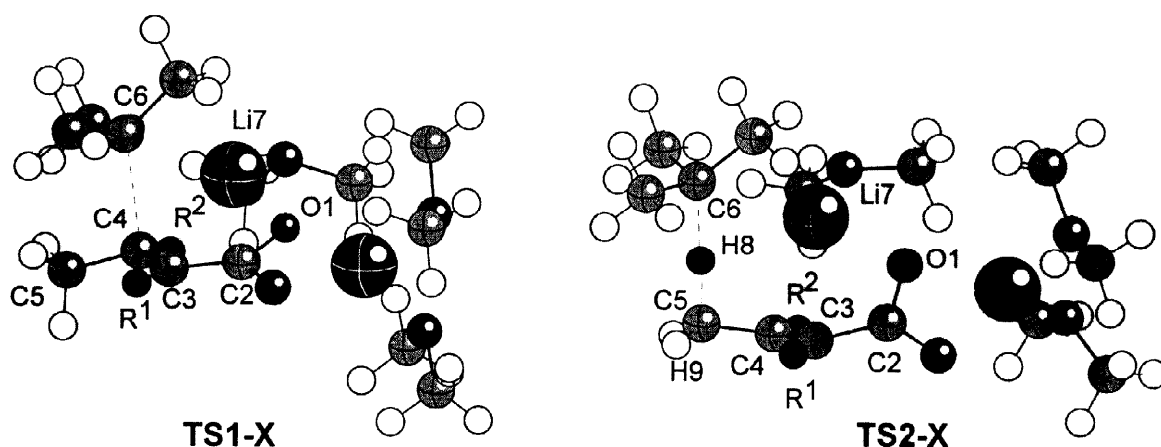
Figure 1. Transition structures TS1-X and TS2-X corresponding to the conjugate addition and E-γ-metallation processes of the acids 5 (X=I, R^1=R^2=H), 13 (X=II, R^1=CH$_3$, R^2=H) and 17 (X=III, R^1=H, R^2=CH$_3$).
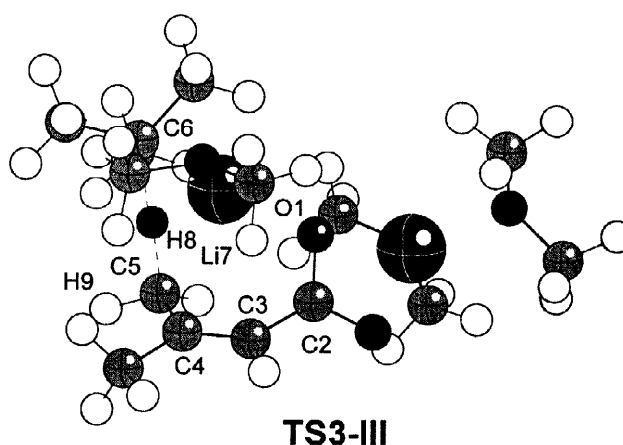

Figure 2. Transition structure TS3-III corresponding to the Z-γ-metallation process of 3-methylbut-2-enoic acid, 17.

Along the E-γ-metallation process (pathway B), the *tert*-butyl anion is abstracting the H8 hydrogen atom of the C5 methyl group while the Li7 atom is being co-ordinated to the C3 carbon, maintaining its co-ordination with the oxygen atom of the carboxylate group (see Figure 1).

At **TS2-I**, corresponding to the E-γ-metallation process of but-2-enoic acid **5**, the lengths of the C6-H8 forming bond and C5-H8 breaking bond are 1.629 Å and 1.282 Å, respectively. The activation energy associated with this process is 20.9 kcal mol^{-1}, being slightly higher than that associated to the nucleophilic attack, in agreement with experimental results. Indeed, although

conjugate addition predominate, deprotonation is observed in the reaction of but-2-enoic acid **5** with *tert*-butyllithium.

Similar geometries are obtained for the **TS1-II** and **TS2-II**, corresponding to the addition and metallation processes of 2-methylbut-2-enoic acid **13** with *tert*-butyllithium. The activation energy for the nucleophilic attack of acid **13** (21.8 kcal mol^{-1}) is slightly higher than the activation energy for the unsubstituted acid **5**, while the activation energy for the metallation process (20.7 kcal mol^{-1}) is almost identical. This accounts for the poor yields of conjugate addition products found when reactions are carried out with the acid **13**, when deprotonation competes to a large extent.

Similar calculations for the **TS1-III** and **TS2-III** of 3-methylbut-2-enoic acid **17** give higher activation energies for both addition and E-γ-metallation processes (30.0 and 22.3 kcal mol^{-1}, respectively), and thus either process should occur more slowly than for any of the former acids. However, when the Z-γ-metallation is considered via **TS3-III** (see Figure 2), the activation energy decrease to 12.7 kcal mol^{-1}. At **TS3-III**, the lengths of the C6-H8 forming bond and C5-H8 breaking bond are 1.586 Å and 1.351 Å, respectively. These bond lengths show that the Z-γ-metallation is more avanced than the E-γ-metallation process. Both TSs, **TS2-III** and **TS3-III**, can be described as eight-membered cycles. However, while the more energetic **TS2-III** implies formation of a strained ring, the more favourable **TS3-III** allows a loose cyclic structure with a much lower activation energy. This finding is in agreement with the experimental fact that for the acid **17** only the deprotonation is observed.

In conclusion, we have shown that primary, secondary and tertiary alkyl- and phenyllithium reagents add successfully to unsubstituted 2-alkenoic acids to afford conjugate addition products. PM3 semiempirical calculations account for the sluggish reactivity of 2-methyl substituted 2-alkenoic acids and the predominant deprotonation of the 3-methyl substituted acids.

Experimental

IR Spectroscopic data were obtained for liquid film or KBr discs, with Bio Rad FTS-7 or Perkin-Elmer 281 spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded for CDCl$_3$ solutions, 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. Melting points were measured with a Reichert apparatus and are uncorrected. Bulb-to-bulb distillations were carried out with a Büchi GKR-50 apparatus; boiling point temperatures stand for temperature of the furnace. 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. 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 °C) was achieved by cooling with a CO_2/acetone bath. Evaporation of solvents was carried out with a vacuum rotary evaporator and a bath at 40 °C. Organolithium reagents were purchased from Aldrich.

General procedures for reaction of carboxylic acids with organolithium reagents

Method A. The unsaturated carboxylic 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 °C. The solution was stirred for 1 to 2 h at the same temperature. Water (30 ml) was added, the solvent was partly evaporated under reduced pressure and the residue extracted with ether. The aqueous layer was acidified, under stirring and ice-water cooling, by slow addition of conc hydrochloric acid, extracted with ethyl acetate and the organic layer dried. Evaporation of the solvent gave crude acids, which were purified by bulb-to-bulb distillation.

Method B. The organolithium reagent (4.5 to 5 mmol) in the commercially available hydrocarbon solution was added slowly with a syringe to a stirred solution of the unsaturated carboxylic acid (2.25 mmol) in THF (20 ml) at -70 °C. The solution was stirred for 1 to 2 h at the same temperature. Quenching and work-up procedure as in Method A.

Heptanoic acid 3a. According the method A, propenoic acid 1 (0.162 g, 2.25 mmol) and *n*-butyllithium (3.2 ml; 1.6 M) gave a colourless oil (0.238 g; 81 %) which was purified by bulb-to-bulb distillation (0.7 mm Hg, oven temperature 104 °C) to give the title acid as a colourless oil (0.125 g; 43 %); δ_H 2.33 (2 H, t, J 7.5 Hz, C2-H), 1.62 (2 H, m, C3-H), 1.30 (6 H, m, 3 x CH_2), 0.87 (3 H, t, J 6.6 Hz, CH_3); δ_C 180.1 (C=O), 34.0, 31.4, 28.7, 24.6 and 22.4 (5 x CH_2), and 13.9 (CH_3) [36, 37].

4,4-Dimethylpentanoic acid 3d. By the same procedure, propenoic acid 1 (0.162 g, 2.25 mmol), and *tert*-butyllithium (2.8 ml; 1.7 M), after the usual work up, gave a colourless oil (0.249 g; 85 %) which on bulb-to-bulb distillation (2 mm Hg, oven temperature 80 °C) gave the title acid as a colourless oil (0.170 g; 58 %); δ_H 2.33 (2 H, t, J 8.6 Hz, C2-H), 1.56 (2 H, t, J 8.6 Hz, C3-H), 0.90 (9 H, s, 3 x CH_3); δ_C 180.6 (C=O), 38.3 (C2), 30.0 (C4), 29.8 (C3) and 28.9 (3 x CH_3) [36, 37].

3-Phenylpropanoic acid 3c. Similarly, propenoic acid 1 (0.162 g, 2.25 mmol) in THF (20 ml) and phenyllithium (2.8 ml; 1.8 M) in THF (30 ml) gave a yellow oil (0.249 g; 74 %) which was purified by bulb-to-bulb distillation (1.5 mm Hg, oven temperature 170 °C) to give the title acid as a colourless oil (0.109 g; 32 %); δ_H 7.24 (5 H, m, Ph), 2.96 (2 H, t, J 7.7 Hz, C3-H), 2.68 (2 H, t, J 7.7 Hz, C2-H); δ_C 179.1 (C=O), 140.1 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.3 (CH, Ar), 35.5 (CH_2) and 30.5 (CH_2) [36, 37].

2-Methylheptanoic acid 4a. According to procedure A, 2-methylpropenoic acid **2** (0.194 g; 2.25 mmol) and n-butyllithium (3.2 ml; 1.6 M) gave an oil (0.20 g; 62 %) which was purified by bulb-to-bulb distillation (3 mm Hg, oven temperature 100°C) to obtain the title acid **4a** as a colourless oil (0.084 g; 26 %). δ_H 2.45 (1 H, m, C2-H), 1.67 (1 H, m, C3-H), 1.42 (1 H, m, C3-H), 1.32 (6 H, m, 3 × CH$_2$), 1.17 (3 H, d, J 6.9 Hz, CH$_3$-C2) and 0.88 (3 H, t, J 6.8 Hz, CH$_3$); δ_C (APT) 183.7 (C=O), 39.4 (C2), 33.5 (CH$_2$), 31.7 (CH$_2$), 26.8 (CH$_2$), 22.5 (CH$_2$), 16.8 (CH$_3$) and 14,0 (C7) [38].

2,4,4-Trimethylpentanoic acid 4c.- 2-Methylpropenoic acid **2** (0.194 g; 2.25 mmol) and tert-buthyllithium (3.2 ml; 1.6 M) as above led to an oil (0,30 g; 93 %) which was purified by bulb-to-bulb distillation (2 mm Hg, oven temperature 90 °C) to give 2,4,4-trimethylpentanoic acid (0.24 g; 74 %). δ_H 2.52 (1 H, m, C2-H), 1.86 (1 H, dd, J 8.6 and 14.2 Hz, C3-H), 1.18 (1 H, dd, J 2 and 14.2 Hz, C3-H), 1.20 (3 H, d, J 6.9 Hz, C2-CH$_3$) and 0.90 (9 H, s, 3 × CH$_3$). δ_C (DEPT) 184.5 (C=O), 47.4 (C3), 36.0 (C2), 30.8 (C4), 29.3 (3 × CH$_3$) and 20.2 (C2-CH$_3$) [39].

2-Methyl-3-phenylpropanoic acid 4d. 2-methylpropenoic acid **2** (0.194 g; 2.25 mmol) was added to phenyllithium (2.8 ml; 1.8 M) according to method A to obtain a yellow oil (0.28 g, 76 %) which on bulb-to-bulb distillation (2 mm Hg, oven temperature 140 °C) afforded 2-methyl-3-phenylpropanoic acid (0.046 g; 12 %). δ_H 7.25 (5 H, m, Ar-H), 3.09 (1 H, dd, J 6.2 and 13.1 Hz, C3-H), 2.78 (1 H, dd, J 8.0 and 13.1 Hz, C3-H) and 1.19 (3 H, d, J 6.9 Hz, CH$_3$). δ_C (APT) 182.3 (C=O), 139.0 (C, Ar), 129.0 (CH, Ar), 128.4 (CH, Ar), 126.4 (CH, Ar), 41.2 (C2), 39.3 (C3) and 16.5 (CH$_3$) [40].

3-Methylheptanoic acid 9a. According to the method A, but-2-enoic acid **5** (0.194 g, 2.25 mmol) and n-butyllithium (3.2 ml, 1.6 M) gave a colourless oil (0.251 g, 75 %) which was purified by bulb-to-bulb distillation (1 mm Hg, oven temperature 70 °C) to give the title acid as a colourless oil (0.211 g; 65 %); δ_H 2.35 (1 H, dd, J 6, 15 Hz, C2-H), 2.14 (1 H, dd, J 8.3, 15 Hz, C2-H) 1.95 (1 H, m, C3-H), 1.29 (6 H, m, 3 x CH$_2$), 0.96 (3 H, d, J 6.6 Hz, CH$_3$), 0.89 (3 H, t, J 6.6 Hz, CH$_3$); δ_C 179.9 (C=O), 41.6 (C2), 36.3 (C4), 30.1 (C3), 29.1 (C5), 22.7 (C6), 19.7(C3-CH$_3$) and 14.0 (CH$_3$) [36, 37].

3,4-Dimethylhexanoic acid 9b. By the same procedure, but-2-enoic acid **5** (0.206 g, 2.40 mmol) and sec-butyllithium (3.8 ml, 1.3 M) gave a colourless oil (0.224 g, 65 %) which on bulb-to-bulb distillation (0.5 mm Hg, oven temperature 90 °C) gave a mixture of diastereoisomers of 3,4-dimethylhexanoic acid **9b** as a colourless oil (0.229 g, 63 %); v_{max} 3300-2500 (O-H) and 1700 (C=O); δ_H 2.36 (1 H, m, C2-H), 2.14 (1 H, m, C2-H), 2.03 (1 H, m, C3-H), 1.35 (2 H, m, C4-H and C5-H), 1.15 (1 H, m, C5-H) and 0.87 (9 H, m, CH$_3$); δ_C 180.6 (C=O), 180.5 (C=O), 39.6 (C2), 39.2 (C4), 38.6 (C4), 37.9 (C2), 34.3 (C3), 33.7 (C3), 27.1 (C5), 25.9 (C5), 17.0 (CH$_3$), 15.6 (CH$_3$), 14.5 (CH$_3$), 14.2 (CH$_3$) and 12.0 (CH$_3$) [41].

3,4,4-Trimethylpentanoic acid 9c. According to the method B, but-2-enoic acid **5** (0.194 g, 2.25 mmol) and *t*-butyllithium (2.8 ml; 1.7 M) gave a colourless oil (0.265 g; 82 %) which was purified by bulb-to-bulb distillation (3 mm Hg, oven temperature 110 °C) to give the title acid as a colourless oil (0.218 g; 69 %); δ_H 2.52 (1 H, dd, J 3.0, 14.5 Hz, C2-H), 1.96 (1 H, dd, J 11.3, 14.5 Hz, C2-H), 1.78 (1 H, m, C3-H), 0.90 (3 H, d, J 6.6 Hz, C3-CH$_3$) and 0.86 (9 H, s, 3 x CH$_3$); δ_C 181.2 (C=O), 39.7 (C3), 37.3 (C2), 32.6 (C4), 27.0 (3 x CH$_3$) and 14.9 (C3-$\underline{C}$H$_3$) [36].

3-Phenylbutanoic acid 9d. According to the method A, but-2-enoic acid **4** (0.194 g, 2.25 mmol) and phenyllithium (2.8 ml; 1.8 M), led to a yellow oil (0.344 g; 93 %) which when distilled (1 mm Hg, oven temperature 110 °C) led to the title acid as a colourless oil (0.283 g; 77 %); δ_H 7.27 (5 H, m, Ph), 3.29 (1 H, m, C3-H), 2.68 (1 H, dd, J 6.9, 15.6 Hz, C2-H), 2.59 (1 H, dd, J 8.3, 15.6 Hz, C2-H) and 1.33 (3 H, d, J 6.9 Hz, CH$_3$); δ_C 178.7 (C=O), 145.4 (C, Ar), 128.6 (CH), 126.7 (CH), 126.5 (CH), 42.6 (C2), 36.1 (C3) and 21.8 (CH$_3$) [36, 37].

3-Ethylheptanoic acid 10a. By the same procedure, *trans*-pent-2-enoic acid **6** (0.225 g, 2.25 mmol) and *n*-butyllithium (3.2 ml, 1.6 M), after usual work, gave a colourless oil (0.241 g; 68 %) which on bulb-to-bulb distillation (0.5 mm Hg, oven temperature 80 °C) gave the title compound as a colourless oil (0.195 g; 55 %); δ_H 2.26 (2 H, d, J 6.8 Hz, C2-H), 1.79 (1 H, m, C3-H) 1.30 (8 H, m, 4 x CH$_2$) and 0.86 (6 H, t, J 7.4 Hz, 2 x CH$_3$); δ_C 180.3 (C=O), 38.6, 36.32, 32.9, 28.7, 26.1 and 22.8 (5 x CH$_2$ and C3), 14.0 (CH$_3$) and 10.7 (CH$_3$) [11].

3-Ethyl-4-methylhexanoic acid 10b. By the same procedure, pent-2-enoic acid **6** (0.225 g, 2.25 mmol) and *sec*-butyllithium (3.8 ml, 1.3 M) gave a colourless oil (0.246 g, 69 %) which was distilled (1 mm Hg, oven temperature 106 °C) to give a mixture of diastereoisomers of **3-ethyl-4-methylhexanoic acid 10b** as a colourless oil (0.199 g, 56 %). Found: (MS, CI+): $(M+1)^+$ 159.1385. C$_9$H$_{19}$O$_2$ requires 159.1383; ν_{max} 3300-2500 (O-H) and 1700 (C=O); δ_H 2.32 (1 H, dd, J 5.1, 15.6 Hz, C2-H), 2.27 (2 H, d, J 6.9 Hz, C2-H), 2.10 (1 H, dd, J 8.4, 15.3 Hz, C2-H), 1.80 (2 H, m, C3-H), 1.39 (6 H, m, C4-H and 2 x CH$_2$), 1.78 (4 H, m, 2 x CH$_2$) and 0.84 (18 H, m, 6 × CH$_3$); δ_C 181.2 (C$_B$=O), 181.0 (C$_A$=O), 41.1 (C$_A$3), 40.6 (C$_B$3), 36.6 (C$_A$4), 36.3 (C$_A$2), 35.8 (C$_B$4), 35.1 (C$_B$2), 26.9 (C$_B$5), 26.0 (C$_A$5), 24.5 (C$_B$H$_2$), 22.6 (C$_A$H$_2$), 15.2 (C$_A$H$_3$), 14.5 (C$_B$H$_3$), 12.1 (C$_A$H$_3$), 12.1 (C$_B$H$_3$), 12.0 (C$_A$H$_3$) and 11.8 (C$_B$H$_3$).

3-Ethyl-4,4-dimethylpentanoic acid 10c. According to the method B, pent-2-enoic acid **6** (0.225 g, 2.25 mmol) and *tert*-butyllithium (2.8 ml, 1.7 M) gave a white solid (0.269 g, 76 %) which was distilled (1 mm Hg, oven temperature 100 °C) to give **3-ethyl-4,4-dimethylpentanoic acid 10c** as a white waxy solid (0.234 g, 67 %), mp 50-52 °C. Found: (MS, CI+): $(M+1)^+$ 159.1385. C$_9$H$_{19}$O$_2$ requires 159.1389; ν_{max} 3300-2500 (O-H) and 1700 (C=O); δ_H 2.44 (1 H, dd, J 5.0, 16.4 Hz, C2-H), 2.12 (1 H, dd, J 6.5, 16.4 Hz, C2-H), 1.60 (2 H, m, C3-H and C4-H), 1.06 (1 H, m, C4-H), 0.93 (3 H, t, J 7.1 Hz, C4-CH$_3$) and 0.88 (9 H, s, 3 x CH$_3$);

δ_C 181.3 (C=O), 46.7 (C3), 35.4 (C2), 33.6 (C3-C), 27.4 (3 x CH$_3$), 23.7 (C4) and 13.2 (C4-CH$_3$).

3-Phenylpentanoic acid 10d. According to the method A, pent-2-enoic acid **6** (0.225 g, 2.25 mmol) and phenyllithium (2.8 ml, 1.8 M)), led to a colourless oil (0.318 g; 79 %) which when distilled (0.5 mm Hg, oven temperature 90 °C) led to the title compound as a colourless oil (0.239 g; 60 %); δ_H 7.23 (5 H, m, Ph), 2.96 (1 H, m, C3-H), 2.63 (2 H, ABX, J$_{AB}$ 12.4 Hz, C2-H), 1.66 (2 H, m, C4-H) and 0.78 (3 H, t, J 7.3 Hz, CH$_3$); δ_C 178.7 (C=O), 143.5 (C, Ar), 128.4 (CH, Ar), 127.4 (CH, Ar), 126.5 (CH, Ar), 43.4 (C2), 41.1 (C3), 29.1 (C4) and 11.8 (CH$_3$) [11].

4-Methyl-3-propylhexanoic acid 11b. Similarly, *trans*-hex-2-enoic acid **7** (0.257 g, 2.25 mmol) and *sec*-butyllithium (3.8 ml, 1.3 M) gave a colourless oil (0.233 g, 60 %) which was distilled (2 mm Hg, oven temperature 92 °C) to give a mixture of diastereoisomers of **4-methyl-3-propylhexanoic acid 11b** as a colourless oil (0.17 g; 44 %). Found: (MS, CI+): (M+1)$^+$ 173.1542. C$_{10}$H$_{21}$O$_2$ requires 173.1542. v_{max} 3300-2500 (O-H) and 1700 (C=O); δ_H 2.25 (3 H, m, C2-H), 2.07 (1 H, dd, J 8.6, 15.2 Hz, C2-H), 1.87 (2 H, m, C3-H), 1.50-1.20 (14 H, m, 6×CH$_2$ and 2×CH-Me)) and 0.85 (18 H, m, 6 x CH$_3$); δ_C 180.9 (C$_B$=O), 180.7 (C$_A$=O), 39.0 (C4-C$_A$H), 38.6 (C4-C$_B$H), 36.9 (C$_A$3), 36.7 (C$_A$2), 36.3 (C$_B$3), 35.3 (C$_B$2), 34.1 (C$_B$4), 32.1 (C$_A$4), 26.8 (C$_B$H$_2$), 26.1 (C$_A$H$_2$), 20.6 (C$_A$5), 20.4 (C$_B$5), 15.1 (C$_A$H$_3$), 14.5 (C$_B$H$_3$), 14.3 (C$_A$H$_3$), 14.2 (C$_B$H$_3$), 12.2 (C$_A$H$_3$) and 12.1 (C$_B$H$_3$).

3-(1,1-Dimethylethyl)hexanoic acid 11c. By the same procedure, hex-2-enoic acid **7** (0.257 g, 2.25 mmol) and t-butyllithium (2.8 ml, 1.7 M), after usual work-up, gave a colourless oil (0.290 g, 75 %) which was purified by bulb-to-bulb distillation (1 mm Hg, oven temperature 110 °C) to give **3-(1,1-dimethylethyl)hexanoic acid 11c** as a colourless oil (0.228 g, 59 %). Found: (MS, CI+): (M+1)$^+$ 173.1542. C$_{10}$H$_{21}$O$_2$ requires 173.1542; v_{max} 3300-2500 (O-H) and 1700 (C=O); δ_H 2.43 (1 H, dd, J 5.3, 16.0 Hz, C2-H), 2.09 (1 H, dd, J 6.4, 16.0 Hz, C2-H), 1.69 (1 H, m, C3-H), 1.71-0.97 (4 H, m, 2 x CH$_2$) and 0.88 (12 H, t, J 7.3 Hz, 4 x CH$_3$); δ_C 181.0 (C=O), 44.6 (C3), 35.9 (C2), 33.4 (C4), 27.2 (3 x CH$_3$), 21.6 (C5) and 14.2 (C5-CH$_3$).

Computing Methods

The computational study was carried out using the PM3 semiempirical method [42], implemented in the MOPAC program [43]. This method renders reliable parameter set for Li element and has been applied to study different organic compounds [34, 35, 44-49]. The molecular geometries of the transition structures (TS) were optimized using optimization routine TS [50]. Stationary points on the potential energy surface (PES) were located by minimizing the gradients of energy to 0.1 kcal mol^{-1}/Å radian. Examination of the TS was

achieved by the evaluation of the Hessian matrix; the nature of these stationary points was established by analytical calculation and diagonalization of the matrix of energy second derivatives, in order to determine the unique imaginary frequency.

Acknowledgements

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