A new reaction between *E*-cinnamaldehyde and phenyllithium. Mechanistic studies

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The reaction of phenyllithium (in excess) with *E*-cinnamaldehyde gives a surprising tandem addition β-alkylation, which can be successfully used for the synthesis of substituted dihydrochalcones. The mechanism by which these unexpected reactions could occur is unknown and experimental and theoretical studies were carried out as a contribution to its understanding.

The observed concentration effects, the surprising changes in the product distribution upon changes in the reaction conditions, the haptomeric structure of the calculated intermediates and the calculated activation energies are consistent with a reaction pathway in which dimeric phenyllithium attacks the *E*-cinnamaldehyde without prior deaggregation. Solvated structures were also calculated using a "dielectric continuum" model for solvent effects.

Introduction

Organolithium compounds show a strong tendency to form oligomeric aggregates in solution, which influences their reactivity[1,2] and, in many cases, also the regio- and stereochemistry of their reactions.[3,4] In solution, average aggregation numbers of several alkyl- and aryllithium compounds have been obtained from freezing-point depression measurements in tetrahydrofuran (THF),[5] and it has been found that phenyllithium has an aggregation grade of 1.6 in THF. In addition NMR studies have shown dimers and monomers of phenyllithium in THF, while in ether tetramers and dimers can coexist.[6,7] In the solid state, $(PhLi–Et_2O)_4$ has been isolated,[8] but several attempts to isolate Lewis-base free phenyllithium have been unsuccessful; the full details of the solid-state structure of PhLi remain unavailable.[9]

The special aggregation features of several organolithium compounds can be conveniently used to direct their reactions towards the desired synthetic goal, in cases where different products would otherwise be obtained.[2] We have recently observed that the carbonylation of lithium amides[10] and the reaction of organolithiums with α,β-unsaturated carbonyl compounds[11] are good examples of this particular behavior. The reaction of phenyllithium with *E*-cinnamaldehyde, **1**, gives, as expected, *E*-1,3-diphenylprop-2-en-1-ol in excellent yield when it is carried out with equimolar amounts of PhLi and **1**.[12] However, we have recently found that when [PhLi]:[**1**] is ≥2 another reaction takes place that can be successfully used for the synthesis of β-substituted dihydrochalcones.[11]

In trying to find out appropriate explanations for the unexpected products, we decided to carry out mechanistic studies on the reaction, from experimental and theoretical viewpoints. Initial complexation between the organolithium and the carbonyl compound has been observed in previous work,[13] and has been proposed as the first step in additions to ketones and aldehydes.[14] The present work concentrates on the further reaction steps; the MNDO semiempirical SCF–MO method[15] was chosen as the most appropriate to carry out the study with hapticity,[16] a considerably important structural property of these types of π-organolithium compounds.[17]

Method of calculation

Calculations were performed at the restricted Hartree–Fock (RHF) level with the MNDO[18] method in the MOPAC 97[19] program, by using the lithium parameters developed by Thiel.[20] MNDO, in spite of its well-known shortcomings,[21] has proven to be reliable for studying large structures of organolithium compounds,[22] their predictions being, in many cases, in close agreement with experimental data resulting from X-ray and/or spectroscopic studies.[23] MNDO tends to overestimate C–Li bond strengths;[24] but it has been shown that the current lithium parameters are capable of embracing aggregation and the particular structures of π-organolithium compounds.[16]

No geometrical constraints were imposed except for the cinnamyl derivative, for which the π system was kept planar throughout. Due to the MNDO overestimation of steric repulsions, the corresponding non-planar structures were found to be somewhat lower in energy. Stationary points were located by use of the EF gradient optimization procedure and the energies were obtained at the more rigorous criteria of the keyword PRECISE, by minimization of the gradient norm at least below 0.05 kcal $Å^{-1}$ deg^{-1}.

Atomic charges were obtained using the Mulliken scheme. Each reported heat of formation is the result of a search for the global minimum starting from several different initial geometries. All the stationary points were characterized as minima or saddle points by calculating and diagonalizing the Hessian matrix and by checking the number of negative eigenvalues.[25]

Results and discussion

Experimental studies

The reaction of PhLi with *E*-cinnamaldehyde, **1**, in THF at 0 °C and protected from light, gives the addition product, **2**, almost exclusively; but, when the reaction conditions are slightly changed, other compounds **3**–**5** are detected in minor amounts (eqn. (1)).

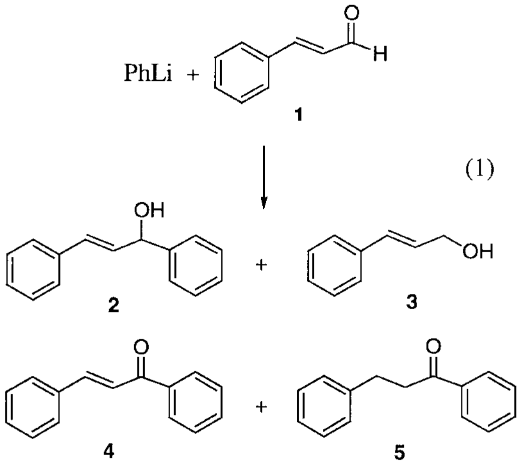
We designed a few experiments to clarify the mechanistic details. The influence of light (at 0 °C) and of the temperature is shown in Table 1. It was observed that using equimolar amounts of reactants in relatively low concentrations, **5** was not detected at all and the distribution of products **2**–**4** was strongly dependent on the reaction conditions.

Higher yields of side products **3** and **4** were observed when the reaction was carried out unprotected from light. Under these conditions, the relative yield of **2** decreases considerably.

Table 1 Addition of PhLi to *E*-cinnamaldehyde, **1**,[a] in THF at several temperatures

	Yields (%)[b]		
T/°C	**2**	**3**	**4**
−78	79	10	11
−20	88	9	3
0	94	0	6
0[c]	70	16	14
20	95	0	5
20[c]	73	8	19

[a] [PhLi]$_0$ = [**1**]$_0$ = 0.07 M. Reaction time 3 h. [b] The yields represent percent conversion. [c] These reactions were carried out unprotected from light.



(1)

The sensitivity to light suggests that radical processes might be involved, especially in those pathways leading to by-products **3** and **4**. According to these results, alternative reaction mechanisms can be proposed (see Scheme 1):

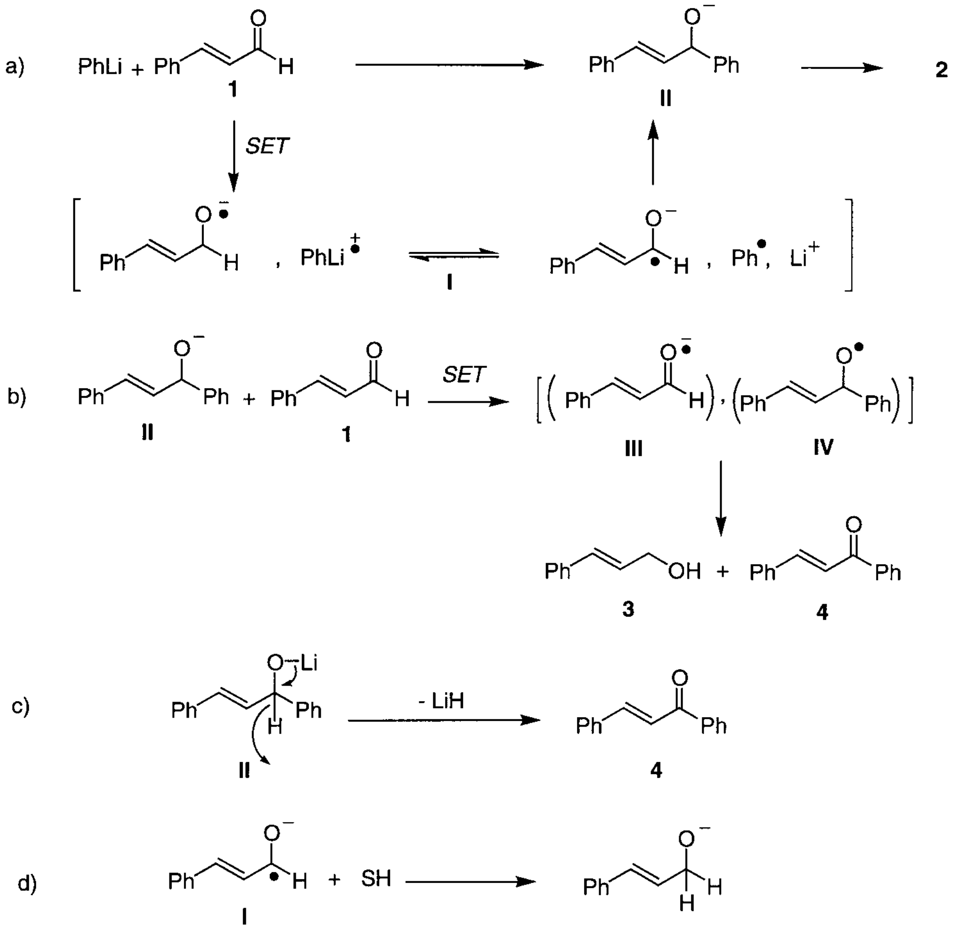
a) Compound **2** can be formed by the classical polar pathway; and/or by an initial electron transfer from PhLi to **1** giving the radical anion–radical cation pair intermediate (**I**), which by reaction within the cage would produce **II**, the anion precursor of **2**.

b) A SET mechanism between **II** and **1** would also explain the production of **3** and **4**. According to this type of Meerwein–Pondorf–Verley mechanism,[26] adduct **II** could react with **1** giving the radical anion **III** and the radical **IV**. H transfer from **IV** to **III** would yield **3** and **4**. Light stimulates electron transfer, and when the reaction is carried out unprotected from light the yields of **3** and **4** increase (see Table 1).

Alternatively, a polar way for the formation of **4** from **II** (pathway c); and a solvent H abstraction by the radical anion **I** for the formation of **3** (pathway d) could be proposed. Since pathway b requires an excess of **1**, and equimolar yields of **3** and **4**, pathways c–d seem more probable for the formation of **4** and **3**, respectively.

To test the proposed mechanisms, the effect of adding radical traps at the beginning of the reaction was examined. Hydroquinone and quinhydrone have previously been found to be effective radical traps in the reaction of naphthyllithium with CO,[27] and results given in Table 2 show that in both cases, only **2** was found.[28]

An additional experiment was carried out with the reaction mixture unprotected from light at −20 °C, followed by quenching with D_2O. In the recovered product **3**, the α carbon was not deuterated, only the OD group attached to C(2). This could indicate that the reaction involves a radical intermediate that abstracts H from the solvent before quenching. Next we



Scheme 1 Alternative pathways in the reactions of PhLi with *E*-cinnamaldehyde, **1**.

Table 2 Effect of the addition of radical traps in the reaction of PhLi with *E*-cinnamaldehyde, **1**,[a] in THF at 0 °C[b]

Additive	Yields (%)[c] **2**	**3**	**4**	**5**	Recovered **1** (%)
None	88	0	11	1	0
Hydroquinone	53	0	0	0	47
Quinohydrone	26	0	0	0	63

[a] $[PhLi]_0 = [\mathbf{1}]_0 = 0.2$ M. Reaction time 3 h. [b] The reactions were carried out unprotected from light. [c] Yields represent percent conversion.

Table 3 Addition of PhLi to *E*-cinnamaldehyde, **1**,[a] in several solvents at 0 °C[b]

Solvent	Yields (%)[c] **2**	**3**	**4**	**5**
THF	94	0	6	0
Toluene	78	0	14	8
Ether	59	22	17	2

[a] $[PhLi]_0 = [\mathbf{1}]_0 = 0.07$ M. Reaction times 3 h. [b] All the reactions were carried out protected from light. [c] The yields represent percent conversion.

attempted to shed light on the mechanism of formation of compound **5**, which seems to be the more interesting feature in the present study.

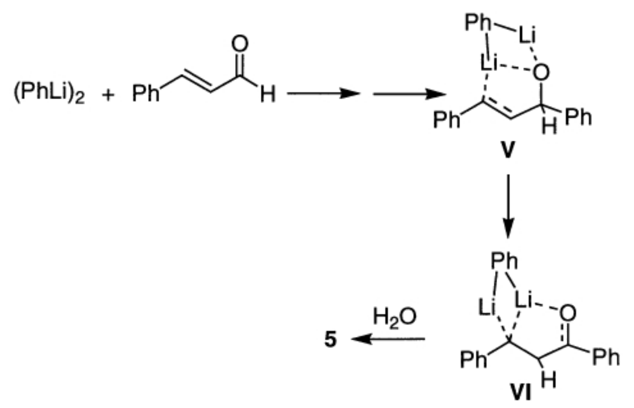
The mechanism proposed in Scheme 1 for the 1,2-addition and for the formation of by-products **3** and **4** can be thought of as occurring with PhLi as monomer or dimer; it is likely that the dimer reacts also without prior deaggregation, as has been observed in other cases.[29] The propensity of organolithium compounds for association in solution and in the solid state is very well known;[4,30] PhLi exists as a dimer–monomer equilibrium in THF solution.[31] When the reaction was carried out in other solvents in which the aggregation state of PhLi is higher, such as ether and toluene, the yields of **3** and **4** increased, and **5** was also obtained (see Table 3).

The influence of the [PhLi]:[**1**] ratio was then investigated. When the reaction was carried out in a ratio [PhLi]:[**1**] = 2 at 20 °C and 7 h reaction time, a brilliant deep violet solution was formed, **2** was no longer obtained, and **5** was formed in 97% yield. The reaction pathway seems to change drastically, **3** was not detected and the yield of **4** largely decreased ([**2**] = [**3**] = 0%, [**4**] = 3%, [**5**] = 97%). The fact that **5** could also be detected when the reaction was carried out in 1:1 ratio in more concentrated solutions (Table 2) seems to confirm that the formation of **5** occurs without deaggregation of PhLi.

Semiempirical studies

We carried out a theoretical study of the above-mentioned unusual reaction between PhLi and *E*-cinnamaldehyde, **1**, in 2:1 ratio. The most relevant part of this plan includes the MNDO study[32] of the probable intermediates in the formation of **5** "*in vacuo*" and also in a "dielectric continuum" (COSMO)[33] to model solvated structures. We calculated different pathways that could lead to the formation of **5** from **1** and PhLi; the reaction pathway briefly depicted in Scheme 2 was found to be the most energetically favorable.[34]

The reaction is formulated as occurring with dimeric PhLi, taking into account the concentration effect and the known structure of phenyllithium in tetrahydrofuran solution.[5] Coordination to **1** through the lithium atom without deaggregation is proposed, followed by the addition of a phenyl moiety, probably through a SET pathway. Coordination of two lithium atoms to the carbonyl oxygen gives the intermediate **V**, which then could undergo a [1,2]-hydride shift giving a new intermediate, **VI**, which would be the precursor of compound **5**. Since the production of **5** increases with longer reaction times and room temperature, this could indicate that the precursor to **5** is formed consecutively to the first intermediate leading to **2**.



Scheme 2 Reaction of PhLi with *E*-cinnamaldehyde, **1**, in [PhLi]:[**1**] = 2.

Structure of the intermediates. The optimized structure of dimer PhLi was obtained from MNDO calculations giving a planar arrangement, with two planar tetracoordinate $RRCLi_2$ *ipso* carbons as previously described.[35] The calculated stabilization energy due to dimerization is high, −72.8 kcal mol^{-1}. Selected geometrical parameters for the calculated intermediates and the transition state are shown in Table 4.

Intermediate V. The first reaction intermediate has a *C*1 symmetry. The optimized geometry is depicted in Fig. 1. Both lithium atoms are bonded to the carbonyl oxygen; they are also bonded to the C(8) (C *ipso*). Interestingly Li(7) is η^2 interacting with the C(3)–C(4) π bond, resulting in a tetracoordinate array. The bond distance between C(3) and C(4), and the fact that the hydrogens bonded to both carbon atoms remain almost in the same plane, indicates the sp^2 nature of these carbons. The distance between C(2) and C(3) corresponds to a single bond length (see Table 4).

C(2) has sp^3 character and is the most positive carbon in this intermediate. Its positive charge even increases during the reaction, especially when the keto form is reached in intermediate **VI**. C(4) has only a poor carbanion character, but surprisingly its negative charge is strongly increased while the lithium atom Li(7) moves towards it, to form the intermediate **VI**; at the same time, the light negative charge of C(3) becomes positive, when the π interaction with Li(7) is lost (see Table 5).

Transition state. The transition state between **V** and **VI** was located and optimized and its structure is shown in Fig. 2. By frequency analysis the stationary state was characterized with only one negative vibrational frequency whose magnitude is −1556 cm^{-1}, which coincides with the reaction coordinate. H(10), at first bonded to C(2), increases its negative charge, having a hydride character in the transition state, suggesting that a 1,2-hydride transfer might occur.

Concomitantly, C(3) and C(4) deviate from planarity; Li(7), which is closer to C(8) than Li(9) (see Table 4), is interacting with C(4) and with C(5) and C(6) (the *ipso* and *ortho* carbons of the phenyl group);[36] and Li(9) is also interacting with C(4), even though it is attached to the oxygen. In this structure, the C(2)–C(3) bond length is shorter than in the intermediates.

Even though the 1,2-hydride shift is orbital symmetry forbidden, the presence of a second phenyllithium is apparently sufficient to catalyze it.[37] Other examples of 1,2-hydride transfer have been previously reported.[38]

Intermediate VI. In this intermediate (see Fig. 3), the bond distance between C(3) and C(4) is close to a single bond, as suggested from the transition state, in which the bond is elongated with regard to species **V** (see Table 4). C(2) and O(1)

Table 4 MNDO heats of formation (ΔH_f, kcal mol^{-1}) and selected distances (Å) for reaction intermediates **V** and **VI** and the transition state (TS)

Species	ΔH_f	O(1)–C(2)	C(2)–C(3)	C(3)–C(4)	Li(7)–C(3)	Li(7)–C(4)	Li(7)–C(5)	Li(7)–C(6)	Li(7)–C(8)	Li(7)–O(1)	Li(9)–O(1)	Li(9)–C(4)	Li(9)–C(8)	C(2)–H(10)	C(3)–H(10)
V	−25.3	1.36	1.57	1.37	2.58	2.36	3.90	3.98	2.05	2.10	1.92	>4	2.05	1.14	2.17
TS	9.2	1.29	1.50	1.43	3.14	2.13	2.38	2.39	2.00	>4	2.04	2.48	2.07	1.38	1.51
VI	−49.2	1.24	1.55	1.55	3.35	2.17	2.28	2.33	2.01	>4	2.15	2.17	2.06	2.16	1.12

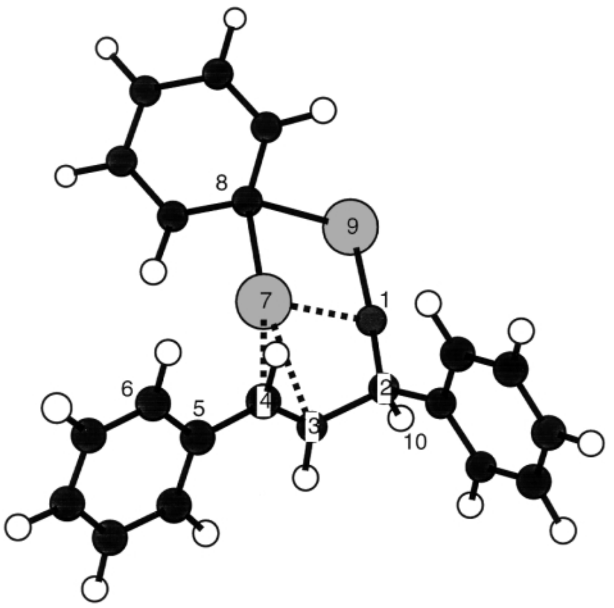


Fig. 1 Optimized structure for the intermediate **V**, as obtained from MNDO calculations. Atoms numbered 7 and 9 are lithiums and atom 1 is oxygen.

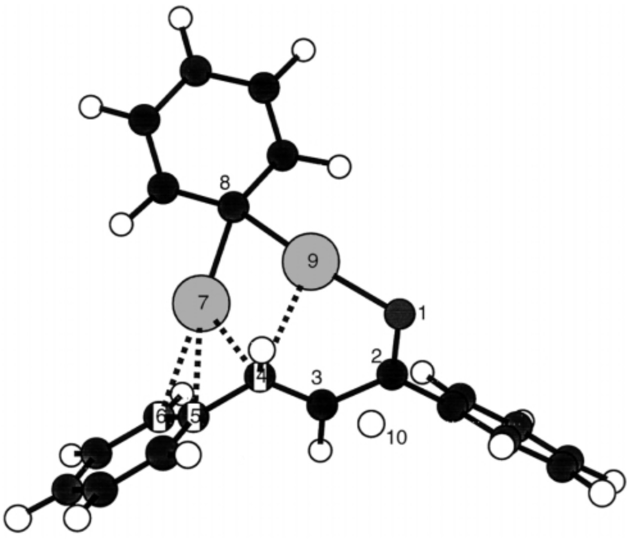


Fig. 2 Optimized structure for the transition state (TS), as obtained from MNDO calculations.

have recovered the carbonyl character (see Tables 4 and 5). C(4) carries a high negative charge, becoming the most negative atom in the molecule; with both Li strongly bonded to it, Li(9) remains interacting with the carbonyl oxygen. The carbanion character of C(4) is very useful for synthetic purposes; we have recently shown the convenience of this intermediate for the synthesis of substituted dihydrochalcones.[11] Li(7) is no longer interacting with O(1), but it is bonded to the aryl carbons C(5) and C(6), in a η^3 haptomeric structure (strongest interaction with C(4), see Fig. 3). The charges of both lithium atoms differ considerably, Li(7) is the most positive making the Li(7)–C(4) bond quite ionic. Finally, it can be observed that **VI** is found preferably in a ketone form.

Scheme 3 gives the reaction energies (kcal mol^{-1}) for the transformations. Strong stabilization of **VI** with respect to **V** can be observed, due probably to the greater coordination of lithium atoms. Even though the detailed reaction energy for the conversion of **V** to **VI** is favorable, since the activation energy for this transformation is rather high (34.5 kcal mol^{-1}), we decided to make calculations including solvent effects.

Solvation of the intermediates. To examine the solvent effect

Table 5 MNDO net atomic charges (q) for selected atoms from dimer PhLi and reaction intermediates

Species	O(1)	C(2)	C(3)	C(4)	C(5)	C(6)	Li(7)	C(8)	Li(9)	H(10)
$(PhLi)_2$	—	—	—	—	—	—	0.35	−0.27	0.35	—
V	−0.56	0.31	−0.06	−0.07	−0.05	−0.04	0.30	−0.27	0.41	−0.03
TS	−0.47	0.33	0.15	−0.37	0.03	−0.11	0.30	−0.28	0.34	−0.14
VI	−0.26	0.32	0.03	−0.33	0.03	−0.12	0.29	−0.26	0.27	0.00

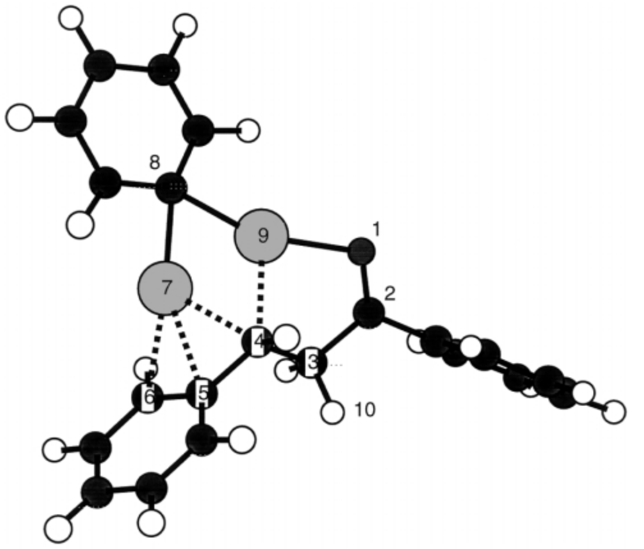
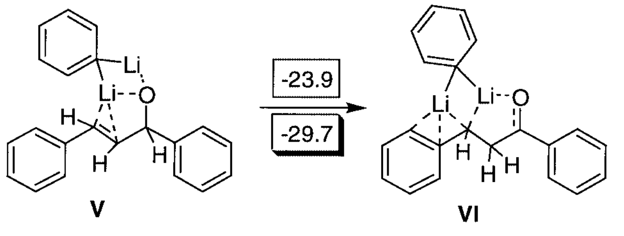


Fig. 3 Optimized structure for the intermediate **VI**, as obtained from MNDO calculations.



Scheme 3 MNDO energy change (kcal mol^{-1}) for the formation of dihydrochalcone, **5**, from the reaction intermediate **V**. Darkened square shows the solvated energy change (COSMO).

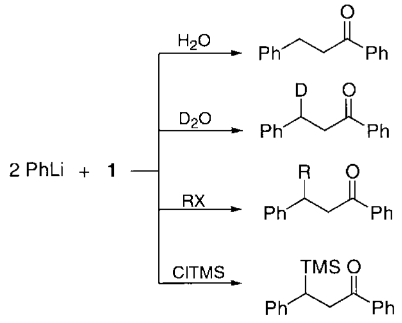
several calculations using discrete solvation[39] and dielectric continuum solvation were carried out. Discrete solvation using dimethyl ether molecules bonded to the lithium atoms as a working model did not account for the expected stabilization of the intermediates, since the structures remained almost unvaried.

Several continuum solvation models have been used successfully for calculations in which solvation effects play a fundamental role.[40] For the present case, the COSMO[32] model accounted reasonably well for the solvation effects observed. This model was successfully used by Saá and coworkers in related calculations of lithium compounds.[17c] The results of minimizations using COSMO for intermediates **V**, **VI** and the transition state are depicted in Table 6. The relative permittivity of THF ($\varepsilon = 7.52$) was used in this approximation.[41]

It can be seen that the relative energies of the intermediates have changed drastically. The reaction energy has a value of −29.7 kcal mol^{-1} (see Scheme 3), and the activation enthalpy decreases its magnitude in almost 11.5 kcal with respect to the unsolvated form. The structures of the intermediates change notably. The interaction of lithium atoms with the carbons becomes weaker, and the hapticity in the intermediates is lower, particularly in **V**. The bond distances Li(7)–C(3) and Li(7)–C(4) are longer and Li(7) is located closer to O(1) in this intermediate: these results are fully consistent with the carbanionic character of C(4) in **VI**.

Further experimental results

Efforts were made to determine the possible existence of such intermediates (see Scheme 4). When the reaction mixture is quenched with D_2O, the β-carbon of the resulting dihydrochalcone is deuterated, which is consistent with the mechanism depicted in Scheme 2 and the precursor **VI** proposed. Similarly, when an alkyl halide RX is added to the reaction flask before hydrolysis, high yields of β-substituted dihydrochalcones are obtained, thus affording a very convenient method for the synthesis of these compounds.[11] On the other hand, independent treatment of **2** with 2 equivalents of PhLi gives **5** as the main product.[42] By treatment of the reaction mixture with 3 equivalents of trimethylchlorosilane, only silylation at the β-carbon was observed, consistent with the less anionic character of the oxygen atom in **VI**.



Scheme 4 Quenching of the reaction mixture ([PhLi] : [**1**] = 2) with different electrophiles.

The above mentioned results are fully consistent with the proposed pathway for the conversion of **1** into **5**; in particular, they are convincing evidence for the existence of a lithium atom bonded to the β-carbon. The rearrangement produced in the reaction of **2** with PhLi, similar to that observed in a reaction with [PhLi] : [**1**] = 2, indicates the likely structure of the intermediate **VI**. Recent works describe the reactions of some cinnamyl derivatives with alkyllithiums in different solvents and in the presence of (−)-sparteine, but they constitute different reactions since under those conditions only carbolithiation takes place and α-substituted compounds are obtained.[43]

Conclusions

The experimental and theoretical studies carried out on the reaction of excess of PhLi with *E*-cinnamaldehyde, **1**, under conditions that allowed complete conversion of **1** into dihydrochalcone, **5**, suggest a reaction pathway in which dimeric PhLi adds to the carbonyl group, giving an intermediate, **V**, which undergoes lithium attack on the β-carbon and a [1,2]-hydride shift producing the precursor of **5**, **VI**. The structures of the likely intermediates involved in the transformation of **1** to **5** were located and minimized. The transition state for the conversion of intermediate **V** to **VI** was also located and supports the proposal.

This work sheds light on the mechanism of a very interesting

Table 6 MNDO heats of formation (ΔH_f, kcal mol^{-1}) and selected distances (Å) for the solvated reaction intermediates and the transition state (TS), using COSMO model

Species	ΔH_f	O(1)–C(2)	C(2)–C(3)	C(3)–C(4)	Li(7)–C(3)	Li(7)–C(4)	Li(7)–C(5)	Li(7)–C(6)	Li(7)–C(8)	Li(7)–O(1)	Li(9)–O(1)	Li(9)–C(4)	Li(9)–C(8)	C(2)–H(10)	C(3)–H(10)
V	−26.5	1.37	1.54	1.34	3.58	3.31	>4	>4	2.04	1.94	1.95	>4	2.05	1.16	2.16
TS	−3.4	1.29	1.50	1.43	3.14	2.13	2.38	2.39	2.00	>4	2.04	2.48	2.07	1.38	1.51
VI	−56.2	1.25	1.55	1.55	3.35	2.19	2.31	2.35	2.05	>4	2.15	2.14	2.06	2.16	1.12

reaction which has wide synthetic utility for the production of substituted dihydrochalcones in a one step–one pot process. MNDO calculations prove to be useful for the prediction of relative trends of this type of organolithium reaction, when the size of the molecular system precludes an *ab initio* calculation.

General reaction procedure

1 mL of a 1 M solution of PhLi in the required dry solvent, contained in a septum-capped round-bottomed reaction flask under nitrogen atmosphere, was cooled to the desired temperature. Then 14 mL of the same solvent and 132 mg (1 mmol) of (*E*)-cinnamaldehyde were added to the stirred solution all at once; by this procedure, both reagents have a final concentration of 0.07 M. Reactions protected or unprotected from light were carried out. The reaction mixtures were worked up by treatment with 0.5 mL of NH_4Cl saturated solution.

Reaction in an excess of PhLi. 3 mL of 1 M PhLi in anhydrous THF were placed in a septum-capped round-bottomed reaction flask, at 20 °C under nitrogen atmosphere. 12 mL of THF and 132 mg (1 mmol) of *E*-cinnamaldehyde were added at once to the stirred solution. The quenching was carried out after 7 h, 1 mmol of the electrophile (RX, D_2O) was added; 3 equivalents were used in the case of TMSCl. The solution was allowed to stir until decoloration, and treated with 0.5 mL of NH_4Cl saturated solution.

Reactions in the presence of radical inhibitors. The reaction was carried out similarly to the general procedure already described, in a reaction flask containing an equimolar amount of the radical inhibitor.

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