Tandem Addition β-Lithiation−Alkylation Sequence on α,β-Unsaturated Aldehydes

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A tandem reaction between *(E)*-cinnamaldehyde, **1a**, and phenyllithium affording β-substituted dihydrochalcones was recently reported. NMR spectroscopic studies on the reaction mixture, as well as isotopic exchange reactions and trapping of two intermediates, provide clues on the several mechanistic steps of this new reaction. Extended studies revealed that β-alkyl-substituted α,β-unsaturated aldehydes and aliphatic lithium reagents did not afford good yields of the tandem reaction products, while aromatic lithium reagents gave good results. The aggregation features of the aryllithium reagents and the extended charged delocalization effects are considered to promote β-selectivity. This approach provides a convenient route for the synthesis of a wide variety of β-alkyl-substituted dihydrochalcones.

Introduction

The tandem or domino reaction has recently been of interest for organic synthesis because it offers a convenient and economical way to prepare desired organic molecules.[1−3] Additionally, combining more than one reaction in one pot usually provides a good solution that will give a better yield and a chance for reactive but difficult-to-generate intermediates to be used in a synthetic sequence.[2]

Organolithium reagents are extremely useful in organic synthesis, and how their specific structures in solution,[4,5] and especially their degree of association,[6,7] affect the reactivity[5,8,9] and in many cases also the regio-[10,11] and stereochemistry[12] of their reactions is the subject of intense research at present. While most organolithium reactants are aggregated under the conditions employed by synthetic chemists, it is not known in many cases whether the observable aggregates react directly or by first deaggregating to transient lower aggregates or monomers.[13−15]

It was usually assumed by synthetic chemists that the "naked" carbanion (the monomer) was more reactive than higher oligomeric states.[16,17] Nevertheless, different complexation effects on *both* the ground state as well as on the transition state(s) could lead to increase or to *decrease* in the reactivity of lower aggregates.[18] Although the structural knowledge of the reacting species in solution is still scarce, recent detailed investigations have demonstrated that, in many cases, the organolithium reagent reacts without previous deaggregation.[19] In addition, complex-induced proximity effects[20] have been advocated to promote remote directed lithiation in some cases, thus providing an expanded synthetic methodology for β-substitution.[12,21]

A thorough survey of the different parameters influencing the addition of phenyllithium to *(E)*-cinnamaldehyde, **1a**, has been recently reported.[22] We demonstrated

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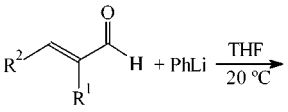
that the reaction is highly sensitive to the reaction conditions and by a careful choice of them, further metalation of the β-carbon can be afforded thus providing a successful route for the synthesis of β-substituted dihydrochalcones in high yields.[1] We report here the results of structural and mechanistic studies that lead to a plausible pathway for this new tandem addition−lithiation−substitution sequence and contribute an efficient synthetic route to new β-substituted dihydrochalcones. The reactions of anisyllithium and of some β-alkyl-substituted α,β-unsaturated aldehydes were also studied to examine the scope of this new synthetic methodology.

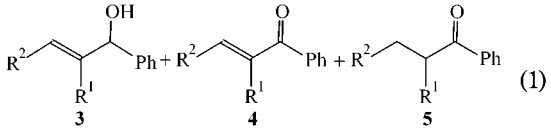
Results and Discussion

Reaction Products. The reaction between **1a** and PhLi, **2**, in dry THF under nitrogen atmosphere and regular conditions gives the expected addition product, *(E)*-1,3-diphenyl-2-propen-1-ol, **3a**, as the main product and variable amounts of *(E)*-chalcone, **4a**, and 1,3-diphenyl-1-propanone, **5a** (eq 1).



1 **2**

a: R^1 = H; R^2 = Ph
b: R^1 = CH_3; R^2 = Ph
c: R^1 = H; R^2 = CH_3CH_2
d: R^1 = CH_3; R^2 = CH_3CH_2



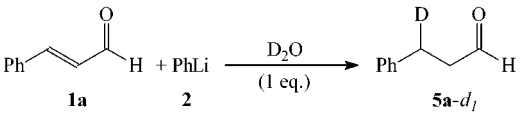
3 **4** **5** (1)

It was previously reported that the product distribution in the reaction mixture is strongly dependent on the reaction conditions; among other factors, variations in the [PhLi]:[**1a**] ratio and/or in the reaction times strongly change the nature and the yield of the different products.[22]

An additional effect is now reported. When 0.07 M PhLi in anhydrous THF is used in a ratio of [PhLi]:[**1a**] = 2, the reaction renders quantitatively **5a** after 12 h at room temperature. However, when the solution is more dilute, [PhLi] = 0.04 M, the regular 1,2-addition product **3a** is favored (78% yield). This suggests that aggregation effects could be strongly involved.

We first selected the reaction of PhLi with **1a** in a 3:1 ratio to carry out some mechanistic studies such as trapping of the intermediates and spectroscopic determinations of their structures. Since even slight variations in the product distribution were considered essential to the purpose of this work, the runs under each reaction conditions were repeated at least three times. The values shown in all of the tables are average results, % variation ± 5%.

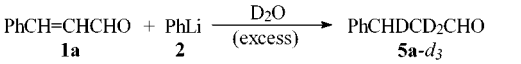
Trapping of Intermediates. Several reactions were carried out at room temperature; the mixtures were allowed to react for 7 h and then quenched. When the reaction was carried out in THF and quenched with 1 equiv of D_2O, a quantitative production of β-deuterated dihydrochalcone, **5a**-d_1, was obtained (eq 2). However,



1a **2** **5a**-d_1 (2)

when the solvent was THF-d_8 and 1 equiv of H_2O was used as the quenching reagent, **5a** was obtained in 73% yield, as the only reaction product. These results undoubtedly shows the position of the lithiated carbon and that there is not exchange with the solvent.

Similar experiments were carried out with excess of the quenching reagent. Both, in THF and THF-d_8 the only isolated product was **5a**-d_3 in 86% and 70% yields, respectively (eq 3). The production of **5a**-d_3 shows the



1a **2** **5a**-d_3 (3)

β-lithiated carbon and, additionally, the acidity of the α-carbon hydrogens that easily exchange with D_2O. To confirm this assumption the same reaction was then carried out in THF-d_8 and quenched with 1 equiv of D_2O, giving **5a**-d_1 in 72% yield. In THF-d_8 no quantitative yields were obtained likely as a result of partial decomposition. Since the reaction was carried out in small amounts, the deuterated solvent has no stabilizer, and it was used without prior distillation. In all of the preceding reactions the products were isolated and fully characterized by melting point, ^{1}H and ^{13}C NMR spectroscopy, and HRMS.

In further experiments, the reaction was carried out using [PhLi]:[**1a**] = 3 in THF at −78 °C, and after 15 min of reaction the mixture was treated with TMSCl. The β-silylated derivative of **3a**, **6**, was obtained in quantitative yield (Scheme 1). To trap the intermediate precursor of the dihydrochalcone, **5a**, the reaction was carried out in THF at 20 °C, allowed to react for 7 h, and then quenched with TMSCl, following the general procedure for the synthesis of β-substituted dihydrochalcones. The β-silylated dihydrochalcone, **7**, was obtained in 98% yield (Scheme 1). This is good evidence for both precursors proposed in the reaction scheme.

NMR Spectroscopic Studies. A NMR spectroscopic investigation of the structures of lithiated intermediates was carried out on the reaction mixture of PhLi and **1a**, at 20 °C, [PhLi]:[**1a**] = 3 in THF-d_8. A full interpretation of the spectroscopic data is difficult to attain without detailed information on the aggregation status of PhLi under the conditions of the experiments. PhLi is one of the most widely studied organolithium reagents. Several X-ray structural determinations,[23] a variety of solution NMR studies (^{13}C, ^{6}Li, and ^{7}Li),[9,24−26] and colligative property measurements[27] have been carried out to determine aggregation states. PhLi occurs in solution in different aggregates (monomer, dimer, and tetramer)

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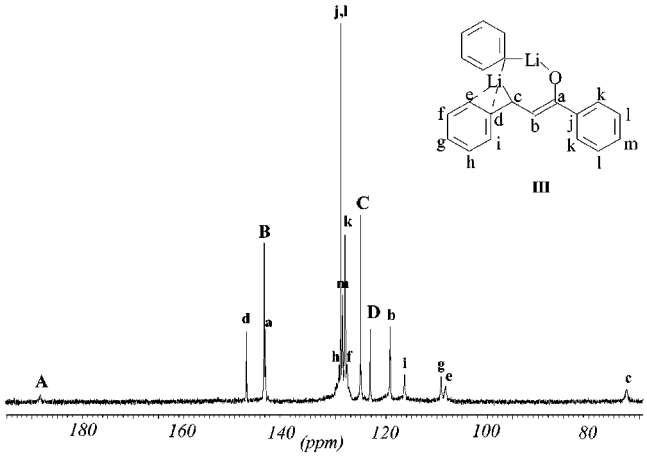

Figure 1. ^{13}C NMR spectrum of the reaction mixture of phenyllithium and *(E)*-cinnamaldehyde, **1a**, [PhLi]:[**1a**] = 3 in THF-d_8. The signals labeled A−D correspond to the carbons in dimeric phenyllithium (A, *ipso*-carbon; B, C, and D, *ortho*-, *meta*-, and *para*-carbons, respectively). The signals marked a−m correspond to the carbons in the proposed intermediate, as shown in the figure.

depending on the solvent, the ligand, and the temperature.[9] In THF solution it is found to be in a monomer−dimer equilibrium. In the ^{13}C NMR spectra, Bauer et al. found chemical shifts for the resonance of C1 at 196.7 ppm for the monomer and 188.7 ppm for the dimer.[26] The signals for the other carbons were 143.4 and 144.6 ppm for C2,6; 124.8 ppm for C3,5 and 120.9 and 123.2 ppm for C4, monomer and dimer, respectively. These data are consistent with Jackman's findings[25] and were fully confirmed in recent aggregation studies of PhLi solution.[9] The ^{13}C NMR spectrum of the reaction mixture in THF-d_8, [PhLi]:[**1a**] = 3, at room temperature shows several signals that are consistent with the structure of an intermediate involving the addition of dimeric PhLi to **1a** (see Figure 1). The signal at 188.30 ppm is clearly assigned to the *ipso*-C atom in a dimeric PhLi as reported,[24−26] and the signals expected for the other carbons in dimeric PhLi at 144.23, 125.02, and 123.13 ppm, respectively, are also observed (labeled A−D in Figure 1). All of the signals for the intermediate were assigned by DEPT and inverse gated heteronuclear decoupling (^{1}H-decoupled spectrum without NOE).

It was reported before that, in contrast to the ^{13}C NMR determinations, the signals of monomeric and dimeric PhLi could not be resolved in the ^{1}H NMR spectrum.[26] This prevents the application of methodologies such as ^{1}H−^{13}C COSY to confirm the assignments. For these reasons, the signals in Figure 1 were confirmed by analogy with the reported chemical shifts of related intermediates. In the case of solid α-(dimethylamino)-benzyllithium, the lithium atom is η^3 coordinated to the *ipso*- and *ortho*-C atoms of the phenyl ring; the η^3 coordination is also preferred in solution.[28,29]

The present intermediate exhibits also an η^3 haptomeric structure, where the lithium atom bonded to the benzylic carbon is interacting with the *ipso*- and *ortho*-carbons of the phenyl ring and with the *ipso*-carbon of the additional phenyllithium. This is in agreement with the intermediate **III** proposed in the reaction scheme and with theoretical calculations.

Table 1. Reactions of *(E)*-Cinnamaldehyde, 1a, and *(E)*-α-Methyl-cinnamaldehyde, 1b, with PhLi, 2, in THF at 20 °C

		reaction	yields,[b] %		
1	[PhLi]:[**1**][a]	time, h	**3**	**4**	**5**
1a	1	4	95	5	
	2	2	21	18	58
	3	2	16	6	66
	3	3	2	12	76
	3	5		10	88
	3	7			92
1b	1	1	65	0[c]	
	1	2	67	13[d]	
	1	4	70	8[e]	
	1	24	73		
	2	2	74	14	7
	2	4	82	7	5
	2	8	76	11	10
	3	4	64	12	12
	3	8	64	12	19
	3	16	67	8	21
	3	24	72	1	27

[a] [**1**]$_0$ = 0.07 M. [b] Determined by quantitative GC using Decalin as internal standard. [c] 20%. [d] 12%. [e] 11% of **1b** recovered.

Table 2. Reactions of *(E)*-2-Pentenal, 1c, and *(E)*-α-Methyl-2-pentenal, 1d, with PhLi

		reaction	yields,[b]%		
1	[PhLi]:[**1**][a]	time, h	**3**	**4**	**5**
1c	1	3	61		
	1[c]	5	60	4	
	1	24	72		
	2[c]	2	79		14
	2	4	88	9	2
	2[c]	4	71	5	24
	2	8	91	8	1
	2	16	86	12	2
	3	2	89	9	2
	3	4	82	15	3
	3	8	74	16	8
	3[c]	8	81	1	18
	3	24	68	12	20
1d	1	2	85		
	1	4	93		
	2	2	86		
	2	4	96		
	2	8	95		
	2	16	100		
	2	24	100		
	3	2	90		
	3	16	94		
	3	24	96		

[a] [**1**]$_0$ = 0.07 M in THF at 20 °C. [b] Determined by quantitative GC using Decalin as internal standard. [c] Reaction carried out at 55 °C.

Influence of the α,β-Unsaturated Aldehyde Structure. The effect of the reaction conditions such as the [**2**]:[**1**] ratio and the time of reaction were first studied using *(E)*-cinnamaldehyde, **1a**, and *(E)*-α-methyl-cinnamaldehyde, **1b**. As shown in Table 1, high yields of the dihydrochalcone, **5a**, were obtained for **1a** after 7 h of reaction in a ratio [**2**]:[**1a**] = 3. In contrast, α-methyl-substitution drastically changes the results. The reaction is less sensitive to the [**2**]:[**1b**] ratio and almost insensitive to the reaction times; in all cases the main product is the alcohol even after 24 h.

When a β-alkyl-substituted α,β-unsaturated aldehyde was used, the alcohol is the main product and a similar inhibitory effect of the α-methyl group on the formation of the tandem product is observed (Table 2). Thus, while

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Table 3. Reaction of *(E)*-Cinnamaldehyde, 1a, and Anisyllithium, 8, in THF

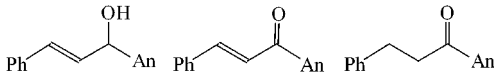
temp	[AnLi]:[**1a**][a]	reaction time, h	yields,[b] % **9**	**10**	**11**
0 °C	1	4	63		
	1.6	4	47		24
	2	4	39	21	32
	2	6	30	22	41
	3	2	31	25	44
	3	4	23	16	41
	3	6	18	25	48
20 °C	1	2	62		
	2	2	33	16	33
	2	4	18	23	55
	2	8	7	21	72
	2	20			87
	2	48			100
	3	4	13	23	64
	3	8		15	77
	3	20			84
	3	32			100

[a] $[\mathbf{1a}]_0 = 0.07$ M. [b] Determined by quantitative GC using Decalin as internal standard.

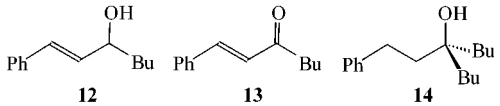
for **1c** even after 24 h reaction in a [**2**]:[**1c**] ratio of 3 only 20% conversion to **5c** is observed, for the α-methyl-substituted aldehyde, **1d**, the inhibition of the second reaction is complete. Regardless of the reaction times and the reagent ratio, no conversion to **5d** could be achieved under any reaction conditions.

Attemps to increase the yield of **5c** by increasing the temperature were unsuccessful. At 55 °C the reaction mixtures became decolored for reaction times longer than 4 or 8 h for ratios [**2**]:[**1c**] = 2 and 3, respectively. Prolonged heating did not improve the production of **5c**.

Influence of the RLi Structure. Table 3 shows the results of the reaction of *(E)*-cinnamaldehyde, **1a**, with anisyllithium, **8**, at 0 and 20 °C (An = 2-methoxyphenyl). The reaction products are *(E)*-1-(2-methoxyphenyl)-3-phenyl-2-propen-1-ol, **9**, *(E)*-1-(2-methoxyphenyl)-3-phenyl-2-propen-1-one, **10**, and 1-(2-methoxyphenyl)-3-phenyl-1-propanone, **11**.



9 **10** **11**



12 **13** **14**

Several reaction conditions were examined. It was found that at 0 °C higher [**8**]:[**1a**] ratios favor formation of **10** and **11**, but the yields are not good. For the reaction at 20 °C, the effect of the reaction times is very clear; for ratios of 2 or 3 the yields of **11** increases at the expense of **9**. The reaction with **8** is slower than with **2**; longer reaction times are needed but a quantitative conversion to **11** could be achieved even with ratios = 2 if enough time for the complete conversion to occur is allowed.

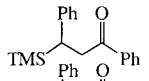
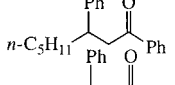
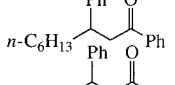
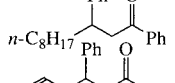
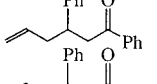
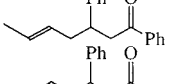
When butyllithium was used (Table 4), the main reaction product was *(E)*-1-phenyl-1-hepten-3-ol, **12**, in all cases. For ratios 2 and 3 the reaction is insensitive to the reaction time, which shows that further reaction of the adduct is strongly inhibited. Relatively small amounts of the result of addition of a second molecule of BuLi to the corresponding ketone were found (compound **14**).

Table 4. Addition of Butyllithium to *(E)*-Cinnamaldehyde, 1a, in THF at 20 °C

[BuLi]:[**1a**][a]	reaction time, h	yields,[b] % **12**	**13**	**14**
1	2	45	8	5
1	6	57	2	6
2	2	89		11
2	6	83		13
2	12	86		14
3	6	83		17
3	12	87		13
3	24	86		9

[a] $[\mathbf{1a}]_0 = 0.07$ M. [b] Determined by quantitative GC using Decalin as internal standard.

Table 5. Addition of PhLi to *(E)*-Cinnamaldehyde, 1a, in THF at 20 °C. Reaction with Electrophiles, RX

RX[a]	β–substituted dihydrochalcone		yields,[b] %
TMSCl	**7**		98
n-C_5H_{11}-Br	**15**		92
n-C_6H_{13}-Br	**16**		88
n-C_8H_{17}-Br	**17**		99
CH_2=CH-CH_2-Cl	**18**		80
CH_2=CH-CH_2-Br			95
CH_3-CH=CH-CH_2-Cl	**19**		77
Ph-CH=CH-Br	**20**		100

[a] $[\mathrm{PhLi}]_0 = 0.21$ M; $[\mathbf{1}]_0 = 0.07$ M; [BrPr] = 0.07 M. [b] Determined by quantitative GC using Decalin as internal standard.

Although only anisyllithium was studied, our experience in related reactions with naphthyl,[30] tolyl, xylyl, and mesityllithium[31,32] suggests that good yields of the tandem products could be also obtained with those aryllithiums since anisyllithium was one of the most difficult reagents to afford good yields of lithiated addition intermediates and it gave good results in the present case.

Addition of Electrophiles. The scope of the tandem addition−*β*-lithiation−alkylation sequence was examined for those cases where good yields of the corresponding 1,3-substituted propanones were obtained. In a previous communication of the reaction of **1a** with PhLi,[1] the reaction with some electrophiles was reported, and some new results are now shown in Table 5.

In all cases, the mixture of PhLi and **1a** was allowed to react for 7 h, and then the desired alkyl halide was added and allowed to react until decoloration (2−8 h depending on RX). It can be observed that the proposed sequence is useful for the preparation of highly pure *β*-alkyl-substituted dihydrochalcones in yields ranging from 77% to 100%. Alkylation could be afforded with alkyl chlorides as well as with bromides; primary halides gave high yields of the substituted products even for relatively long normal chains (e.g., $C_8H_{17}Br$). Hindered alkyl bromides, such as isopropyl (100%) and cyclohexyl

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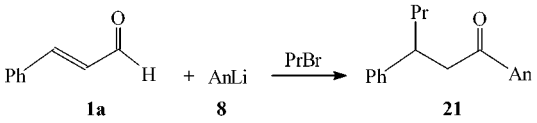
Table 6. Addition of Anisyllithium, 8, to *(E)*-Cinnamaldehyde, 1a, in THF at 20 °C. Reaction with Propyl Bromide

[AnLi]:[**1a**][a]	reaction time, h	yields,[b] %			
		9	**10**	**11**	**21**
2	8	10	16	32	33
2	20	9		36	44
2	32			31	69
3	8	9	14	24	35
3	16	15	4	34	47
3	24	5	4	22	65
3	32			21	79
3	48			19	81

[a] $[\mathbf{1a}]_0 = 0.07$ M; [BrPr]= 0.07 M. [b] Determined by quantitative GC using Decalin as internal standard.

(80%), gave also good results, and allyl (**18**, **19**), vinyl (**20**), and TMS β-substituted dihydrochalcones, **7**, could be easily obtained with high to excellent yields.



1a **8** **21** (4)

Table 6 shows the results of the addition of propyl bromide to the reaction of **1a** with anisyllithium, **8** (eq 4). As observed before, the reaction is slower than with PhLi. Good yields of the alkylated product, **21**, could be achieved using a ratio = 3 and reaction times >30 h; some amount of **11** remains even after 48 h of reaction.

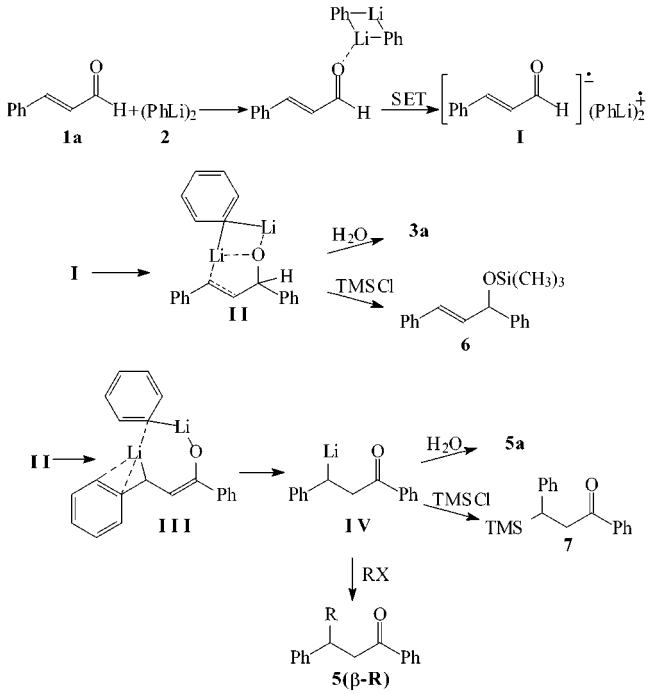
Reaction Mechanism. In light of the preceding results it is clear that aryl structures in both the organolithium reagent and in the β-substituted α,β-unsaturated aldehyde are needed for this new tandem addition−β-lithiation−alkylation reaction to occur in synthetically appealing yields.

The present results allow proposal of a plausible mechanism for the tandem reaction, which will be discussed for *(E)*-cinnamaldehyde, **1a**, and PhLi as shown in the Scheme 1. Taking into account the observed effects and previous accounts on other reactions,[14,15,18,19] a dimeric PhLi is considered the reactant species for the mechanism of the reaction in a [PhLi]:[**1a**] ratio equal to 3. Although several species are likely present in the reaction mixture, only the unsolvated dimer is considered in the reaction scheme for the sake of simplicity.

The initiation step could be complexation of PhLi to **1a** by a precoordination of the lithium atoms to the carbonyl oxygen; this coordination of lithium atom to carbonyl oxygen would be responsible for 1,2 addition.[33] Complex formation between the reactants has also been invoked in recent examinations of how lithiations actually occur,[34] especially when the organic precursor contains functionalities such as a C=O or P=O unit.[35,36]

The next step is an electron transfer from PhLi to **1a**, giving the radical anion−radical cation pair **I**. Electron transfer from PhLi to carbonyl compounds[37−39] and to other electron acceptor functionalities[31] has been recently proved to be the first step in addition reactions. Only in

Scheme 1. Reaction Scheme



the case of the lithium pinacolone enolate addition to benzaldehyde, determination of activation energies[40] and of kinetic isotope effects[41] seems to indicate that the reaction proceeds via a polar mechanism. In the present case, the development of a stable intense violet color strongly suggests the formation of radicals. The recently studied addition of PhLi to **1a**, under normal conditions, which gives the α-phenyl-cinnamyl alcohol, **3a**, has been also shown to occur by an electron-transfer mechanism.[22] Reaction of the radical anion of intermediate **I** with the phenyl radical cation within the solvent cage leads to the 1,2-adduct, anion **II**, which renders **3a** upon hydrolysis.

The remarkable feature in the present reaction would be the coordination of a second lithium atom to the β-carbon in the adduct **II**, leading to a cyclic intermediate **III**, which disrupts to intermediate **IV**, the lithiated precursor of **5a**. It was shown that longer reaction times favored formation of **5a** at expenses of **3a**; this suggests that the conversion of intermediate **II** to **III** would be the slow step in the production of **5a**. In fact, when the reaction is quenched after relatively short reaction times, the 1,2-adduct is the major compound in the reaction mixture, and the silylated derivative of **3a** is obtained after 15 min of reaction at − 78 °C by quenching with TMSCl. On the contrary, when the reaction is allowed to stand for longer times, the results indicate that the intermediate giving **3a** slowly transforms into the precursor of **5a**. The transition state from the **II** → **III** conversion has been calculated by semiempirical methods

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and found to be a real transition state. 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.[42] The calculated transition state exhibits also an η^3 haptomeric structure. The hydrogen atom, at first bonded to the oxygen bearing carbon, has a hydride character in the transition state, suggesting that a 1,2-hydride transfer might occur.

It was shown by the NMR spectroscopic studies, as well as by the theoretical calculations, that a strong interaction exists between the lithium atom bonded to the β-carbon in the intermediate **III** and the *ipso*- and *ortho*-carbons of that phenyl ring. Extended charge delocalization between the three phenyl groups is also clear, and both effects should contribute to the driving force for the conversion of **II** to **III** and the stabilization of the intermediate **III**. Although this 1,2-hydride shift is orbital symmetry forbidden, the presence of the second phenyllithium provides sufficient driving force to catalyze it. This would explain why aliphatic α,β-unsaturated aldehydes and aliphatic lithium reagents fail to afford the tandem reaction. The structure of **5a**-d_3 determined by quenching the reaction mixture with an excess of D_2O shows the involvement of the acid α-hydrogens in the extended electronic delocalization, which is consistent with the observed retarding effects of the methyl groups in the α-position.

A similar kinetic deprotonation of β-aryl secondary amides has been rationalized in terms of a complex-induced proximity effect (CIPE),[20,43] and the methodology was recently applied to synthesize enantioenriched β-aryl β-substituted amides, acids, and lactones.[44] In the present case, the lithiated intermediate **IV** was shown to react with electrophiles to provide the β-substituted products with high selectivity.

Addition of alkyllithiums on cinnamyl substrates has received a great deal of interest in the last years,[45,46] and it has been recently applied to the synthesis of asymmetric cinnamyl derivatives[47] and chiral disubstituted cyclopropanes[48] by running the reaction in the presence of (−)-sparteine. Nevertheless, the reaction differs from the present case, since addition of cinnamyl alcohol to a solution of BuLi under the conditions described by different groups[45,47,48] gives attachment of a butyl moiety to the α-*carbon*, while under the conditions described in the present work lithiation of the β-*carbon* is observed instead.

In the Scheme 1 only the species $(PhLi)_2$ is considered, but mechanisms involving monomer or dimer are plausible, taking into account that in the monomer−dimer equilibrium probably both of them (and even others) are operating; no distinction is possible in the light of the present structural knowledge. It has been recently reported the role that the lithium ion plays in the activation of organic substrates,[49] and it could be also likely operating in the present case, stabilizing intermediate **IV** by coordination to the lone pair on the heteroatom. Although in light of the given evidence a stepwise mechanism cannot be ruled out for the present case, on the basis of the observed concentration effects, the ^{13}C NMR results, the calculated transition state, and the experimental fact that **3a**, as well as the dihydrochalcone, **5a**, do not afford the same results under similar reaction conditions, the mechanism proposed in the scheme is preferred.

Conclusion

The present work provides methodology for a convenient one-pot syntheses of β-alkyl-substituted dihydrochalcones in high yields from the reaction of *(E)*-cinnamyl aldehydes with aryllithiums and suitable electrophiles in a tandem addition−β-alkylation−substitution sequence. Several evidences such as NMR spectroscopic determinations, trapping of two intermediates, and theoretical calculations of transition states are consistent with a mechanism involving electron transfer from dimeric phenyllithium to the aldehyde, addition to the carbonyl group followed by a further attack of the second phenyllithium to the β-carbon affording a β-lithiated adduct able to react with suitable electrophiles. β-Alkyl-substituted α,β-unsaturated aldehydes as well as aliphatic lithium reagents failed to afford the tandem reaction, giving mostly the regular adduct.

Experimental Section

General Methods. All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.[50] All compounds reported here are fully characterized by melting point (when applicable), mass spectrometry (using a gas chromatograph coupled to the BG Trio-2 mass spectrometer), and nuclear magnetic resonance spectroscopy (determined on a Brucker 200 spectrometer operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C and a Brucker 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C). The ^{1}H chemical shifts are referenced relative to TMS, and the ^{13}C chemical shifts are referenced relative to $CDCl_3$ at $\delta = 77.0$ and THF-d_8 at $\delta = 67.5$. High-resolution mass spectra were measured on a ZAB-SEQ4F mass spectrometer. The GC analyses were carried out on a 5890 Hewlett-Packard gas chromatograph, using a HP-5 column.

Materials. Tetrahydrofuran (THF) and hexane were purified as previously described[51] and were distilled from dark blue solutions of sodium/benzophenone ketyl under nitrogen immediately prior to use. Benzophenone (Aldrich) was 99% pure and was used after recrystallization from ethanol. Commercial *(E)*-cinnamaldehyde, *(E)*-α-methyl-cinnamaldehyde, *(E)*-2-pentenal, and *(E)*-α-methyl-2-pentenal were distilled prior to use. Butyllithium, solid phenyllithium, and anisyllithium were prepared as previously described.[52] The concentration of BuLi was determined by the double titration method described

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before.[53] The concentration of PhLi was determined by reaction with diphenylacetic acid.[54] All glassware, syringes, and needles were dried in a vacuum oven and cooled in a desiccator. Compounds **3a**,[55] **4a**,[56] **5a**,[57] and **13**[58] were identified spectroscopically and characterized by their melting points against samples independently prepared by reported methods. The physical constants and spectroscopic data of compounds **4c**,[59] **5b**,[60] **5c**,[61] and **12**[62] were in agreement with the literature data. The new alkyl-substituted dihydrochalcones were synthesized according to the general procedure previously described.[1]

Isotope Exchange Reactions. (a) Typical Procedure for the Addition in THF. A total of 15 mL of 0.2 M PhLi in anhydrous THF was placed in a septum-capped round-bottomed reaction flask under a nitrogen atmosphere at room temperature. Then 132 mg (1 mmol) of *(E)*-cinnamaldehyde was added at once to the stirred solution. After 7 h, 20 mg (1 mmol) of D_2O was added. The solution was dried with Na_2SO_4, diluted to volume with distilled methanol, and quantified by GC. The product was isolated by TLC and identified by melting point, ^1H and ^{13}C NMR spectroscopy, and HRMS. A 95% yield of **5a**-d_1 was determined.

(b) Typical Procedure for the Addition in THF-d_8. To 1 mL of 1.5 M PhLi in THF-d_8 99% was added 66 mg (0.5 mmol) of *(E)*-cinnamaldehyde, and the mixtures was allowed to react for 7 h and then quenched with excess of D_2O. The organic layer was dried with Na_2SO_4, and a determination procedure similar to that described in (a) above gave 70% yield of compound **5a**-d_3.

^{13}C NMR Spectrum of the Intermediate III. The ^{13}C NMR spectra for the intermediate were determined using a Bruker 500 spectrometer at 125 MHz. The spectra were determined as follows. To a solution of 84 mg (1 mmol) of PhLi in 1 mL of THF-d_8 in a 5-mm NMR tube capped with a septum at 0 °C under a nitrogen atmosphere was added 44 mg (0.3 mmol) of freshly distilled (*E*)-cinnamaldehyde. The solution was vigorously shaken to ensure complete mixing. After 7 h, the sample was allowed to equilibrate to the temperature of the probe over 15 min before the ^1H decoupled ^{13}C NMR spectrum was obtained. The center peak of the downfield quintet of the THF-d_8 was used as the reference peak and was set to be at $\delta = 67.50$. ^{13}C NMR (125 MHz, THF-d_8) δ 72.49, 108.25, 109.14, 116.34, 119.25, 127.58, 128.06, 128.58, 128.93, 129.28, 144.07, 147.60.

***(E)*-2-Methyl-1,3-diphenyl-2-propen-1-ol (3b).** Oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, 3H, J = 1.3 Hz), 5.29 (s, 1H), 6.78 (s, 1H), 7.21 (m, 1H), 7.32 (m, 7H), 7.44 (dd, 2H, J = 1.0 and 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.92, 79.34, 125.84, 126.40, 127.41, 128.02, 128.28, 128.95, 137.50, 139.62, 142.17. HRMS m/z for $C_{16}H_{16}O$ calcd 224.1201, found 224.1205.

***(E)*-1-Phenyl-2-penten-1-ol (3c).** Oil.^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.4 Hz), 2.08 (m, 2H), 5.17 (d, 1H, J = 6.8 Hz), 5.67 (ddt, 1H, J = 1.6, 6.8 and 15.5 Hz), 5.81 (dt, 1H, J = 6.0 and 15.5 Hz), 7.27 (m, 1H), 7.36 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.30, 25.19, 75.26, 126.16, 127.49, 128.46, 131.34, 134.31, 143.45. HRMS m/z for $C_{11}H_{14}O$ calcd 162.1045, found 162.1049.

***(E)*-2-Methyl-1-phenyl-2-penten-1-ol (3d).** Oil.^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.6 Hz), 1.47 (s, 3H), 2.07 (m, 2H) 5.10 (s, 1H), 5.63 (t, 1H, J = 7.1 Hz), 7.24 (m, 1H), 7.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.77, 13.98, 20.90, 79.24, 126.19, 127.17, 128.16, 128.86, 136.14, 142.49. HRMS m/z for $C_{12}H_{16}O$ calcd 176.1201, found 176.1205.

***(E)*-2-Methyl-1,3-diphenyl-propenone (4b).** Oil.^1H NMR (200 MHz, $CDCl_3$) δ 1.93 (s, 3H), 7.26 (m, 3H), 7.54 (m, 5H), 7.69 (s, 1H), 7.90 (d, 2H, J = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.30, 126.82, 128.55, 128.75, 129.90, 130.58, 131.23, 134.85, 136.03, 139.90, 200.09. HRMS m/z for $C_{16}H_{14}O$ calcd 222.1045, found 222.1050.

1,3-Diphenyl-[3-^{2}H]-propan-1-one (5a-d_1). White solid, mp 69 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 3.07 (t, 1H, J = 7.1 Hz), 3.29 (d, 2H, J = 7.5 Hz), 7.27 (m, 5H), 7.47 (m, 3H), 7.95 (dd, 2H, J = 1.1 and 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.81 (t, J_{C-D}=19.7 Hz), 40.32,126.08, 128.00, 128.37, 128.48, 128.53, 132.98, 136.92, 141.23, 157.38, 199.15. MS m/z: 211 (M^+), 106 ($M^+ - PhC_2H_3D$), 105 ($M^+ - PhCO$), 92 ($M^+ - PhCOCH_2$). HRMS m/z for $C_{15}H_{13}DO$ calcd 211.1108, found 211.1103.

1,3-Diphenyl-[2,2,3-$^2H_3$]-propan-1-one (5a-d_3). White crystals, mp 64 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 3.05 (s, 1H), 7.27 (m, 5H), 7.49 (m, 3H), 7.95 (dd, 2H, J = 1.5 and 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.68 (m), 30.87 (m), 126.11, 128.03, 128.26, 128.39, 128.51, 128.59, 130.03, 132.37, 133.03, 136.03, 141.22, 199.23. MS m/z: 213 (M^+), 105 ($M^+ - PhCHD_3$), 92 ($M^+ - PhCOCHD_2$). HRMS m/z for $C_{15}H_{11}D_3O$ calcd 213.1233, found 213.1240.

***(E)*-1,3-Diphenyl-1-trimethylsilyloxy-2-propene (6).** Oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 9H), 5.20 (d, 1H, J = 6.2 Hz), 6.17 (dd, 1H, J = 6.2 and 15.7 Hz), 6.47 (d, 1H, J = 15.7 Hz), 7.18 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.27, 75.52, 126.19, 126.54, 127.19, 127.46, 128.26, 128.48, 129.26, 132.87, 136.86, 143.55. HRMS m/z for $C_{18}H_{22}OSi$ calcd 282.1440, found 282.1445.

1,3-Diphenyl-3-trimethylsilyl-1-propanone (7). White crystals, mp 84−84.5 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 9H), 2.90 (dd, 1H, J = 5.1 and 9.5 Hz), 3.29 (dd, 1H, J = 5.1 and 16.8 Hz), 3.54 (dd, 1H, J = 9.5 and 16.8 Hz), 7.07 (d, 3H, J = 7.3 Hz), 7.2 (m, 2H), 7.45 (m, 3H), 7.90 (d, 2H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.89, 31.24, 39.03, 124.57, 127.37, 127.89, 128.05, 128.43, 132.68, 137.21, 143.17, 199.12. HRMS m/z for $C_{18}H_{22}OSi$ calcd 282.1440, found 282.1444.

***(E)*-1-(2-Methoxy-phenyl)-3-phenyl-2-propen-1-ol (9).** Oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.91 (br s, 1H), 3.85 (s, 3H), 5.58 (d,1H, J = 6.0 Hz), 6.46 (dd, 1H, J = 6.1 and 16.0 Hz), 6.64 (d, 1H, J = 16.0 Hz), 6.89 (d, 1H, J = 8.2 Hz), 6.96 (t, 1H, J = 7.4 Hz), 7.21 (m, 2H), 7.28(m, 3H), 7.36 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.42, 71.31, 110.79, 120.94, 126.50, 127.43, 127.45, 128.44, 128.76, 129.89, 130.96, 136.96, 156.70. HRMS m/z for $C_{16}H_{16}O_2$ calcd 240.1150, found 240.1155.

***(E)*-1-(2-Methoxy-phenyl)-3-phenyl-propenone (10).** White crystals, mp 65−66 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.84 (d, 1H, J = 15.9 Hz), 7.23 (m, 7H), 7.44 (m, 1H), 7.58 (d, 1H, J = 16 Hz), 7.86 (d, 1H, J = 7.5 Hz) ^{13}C NMR (60 MHz, $CDCl_3$) δ 55.57, 114.00, 121.15, 124.01, 127.60, 128.64, 128.75, 129.87, 131.05, 134.90, 135.23, 142.80, 158.82, 191.56. HRMS m/z for $C_{16}H_{14}O_2$ calcd 238.0994, found 238.0996.

1-(2-Methoxy-phenyl)-3-phenyl-propan-1-one (11). White crystals, mp 84−85 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 3.02 (t, 2H, J = 7.8 Hz), 3.30 (t, 2H, J = 7.8 Hz), 3.87 (s, 3H), 6.95 (d, 1H, J = 8.2 Hz), 6.99 (t, 1H, J = 7.5 Hz), 7.23 (m, 5H), 7.44 (dt, 1H, J = 1.8 and 7.5 Hz), 7.68 (dd, 1H, J = 1.8 and 7.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.48, 45.38, 55.48, 111.51, 120.67, 125.87, 128.37, 128.43, 130.33, 133.35, 141.72, 158.52, 201.70. HRMS m/z for $C_{16}H_{16}O_2$ calcd 240.1150, found 240.1153.

1,3-Diphenyl-1-octanone (15). White crystals, mp 59−60 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 6.6 Hz), 1.22 (m, 6H), 1.64 (m, 1H), 1.71 (m, 1H), 3.22 (dd, 1H, J = 7.4 and 16.3 Hz), 3.27 (dd, 1H, J = 6.4 and 16.4 Hz), 3.32 (m, 1H), 7.17 (t, 1H, J = 7.2 Hz), 7.22 (d, 2H, J = 6.9 Hz), 7.27 (t, 2H, J = 7.6 Hz), 7.41 (t, 2H, J = 7.7 Hz), 7.52 (t, 1H, J = 7.3 Hz), 7.89 (d, 2H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.99, 22.47, 27.13, 31.75, 36.29, 41.33, 45.99, 126.19, 127.55, 128.03,

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128.39, 128.49, 132.83, 137.34, 145.01, 199.19. HRMS *m*/*z* for $C_{20}H_{24}O$ calcd 280.1827, found 280.1823.

1,3-Diphenyl-1-nonanone (16). White crystals, mp 51−52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, J = 6.8 Hz), 1.20 (m, 8H), 1.64 (m, 1H), 1.72 (m, 1H), 3.24 (m, 2H), 3.32 (m, 1H), 7.17 (t, 1H, J = 7.1 Hz), 7.22 (d, 2H, J = 6.9 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.41 (t, 2H, J = 8 Hz), 7.52 (t, 1H, J = 7.4 Hz), 7.89 (d, 2H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.01, 22.58, 27.44, 29.22, 31.68, 36.35, 41.35, 46.00, 126.20, 127.56, 128.03, 128.38, 128.49, 132.83, 137.34, 145.02, 199.2. HRMS *m*/*z* for $C_{21}H_{26}O$ calcd 294.1984, found 294.1991.

1,3-Diphenyl-1-undecanone (17). White crystals, mp 44.5−45.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 3H, J = 7.1 Hz), 1.19 (m, 12H), 1.64 (m, 1H), 1.71 (m, 1H), 3.21 (dd, 1H, J = 7.3 and 16.2 Hz), 3.26 (dd, 1H, J = 6.4 and 16.2 Hz), 3.32 (m, 1H), 7.16 (t, 1H, J = 7.2 Hz), 7.22 (d, 2H, J = 6.9 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.41 (t, 2H, J = 7.7 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.89 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.06, 22.62, 27.46, 29.22, 29.41, 29.54, 31.82, 36.34, 41.35, 46.00, 126.20, 127.56, 128.03, 128.39, 128.49, 132.83, 137.34, 145.03, 199.20. HRMS *m*/*z* for $C_{23}H_{30}O$ calcd 322.2297, found 322.2302.

1,3-Diphenyl-5-hexen-1-one (18). White crystals, mp 68 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.48 (m, 2H), 3.30 (dd, 2H, J = 2.9 and 6.5 Hz), 3.49 (m, 1H), 5.00 (m, 2H), 5.70 (m, 1H), 7.26 (m, 5H), 7.46 (m, 3H), 7.91 (d, 2H, J = 6.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.76, 40.73, 44.60, 116.77, 126.37, 127.55, 128.01, 128.42, 128.50, 132.84, 136.26, 144.37, 206.71. HRMS *m*/*z* for $C_{18}H_{18}O$ calcd 250.1358, found 250.1360.

***(E)*-1,3-Diphenyl-5-hepten-1-one (19).** White crystals, mp 54.5−55 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (M, 3H), 2.39 (m, 2H), 3.29 (m, 2H), 3.43 (m, 1H), 5.37 (m, 2H), 7.23 (m, 5H), 7.49 (m, 3H), 7.90 (d, 2H, J = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.84, 39.62, 41.32, 44.56, 126.21, 127.34, 127.53, 127.99, 128.34, 128.48, 128.72, 132.82, 137.34, 144.75, 199.11. HRMS *m*/*z* for $C_{19}H_{20}O$ calcd 264.1514, found 264.1518.

***(E)*-1,3,5-Triphenyl-4-penten-1-one (20).** White crystals, mp 35−37 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (ddd, 2H, J = 7.1 and 16.6 Hz), 4.30 (dt, 1H, J = 5.0 and 7.1 Hz), 6.40 (dd, 2H, J = 5.0 and 16.0 Hz), 7.21 (m, 4H), 7.32 (m, 6H), 7.34 (t, 2H, J = 7.5 Hz), 7.54 (dt, 1H, J = 1.3 and 8 Hz), 7.94 (dd, 2H, J = 1.3 and 8.3 Hz).[63] ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.97, 44.54, 126.24, 126.62, 127.22, 127.30, 127.76, 128.07, 128.43, 128.59, 128.66, 130.11, 132.60, 133.03, 137.20, 143.31, 198.15. HRMS *m*/*z* for $C_{23}H_{20}O$ calcd 312.1514, found 312.1521.

1-(2-Methoxyphenyl)-3-phenyl-1-hexanone (21). White crystals, mp 48 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, J = 7.2 Hz), 1.17 (m, 2H), 1.61 (m, 2H), 3.30 (m, 3H), 3.85 (s, 3H), 6.91 (d, 1H, J = 8.4 Hz), 6.93 (dt, 1H, J = 1.0 and 7.6 Hz), 7.15 (m, 3H), 7.24 (m, 2H), 7.40 (ddd, 1H, J = 2.0; 7.4 and 8.4 Hz), 7.46 (dd, 1H, J = 2.0 and 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.98, 20.56, 38.75, 41.25, 50.94, 55.43, 111.35, 120.62, 125.96, 127.64, 128.19, 130.10, 132.98, 145.28, 158.08, 202.02. HRMS *m*/*z* for $C_{19}H_{22}O_2$ calcd 282.1620, found 282.1626.

Note. One of the referees suggested to perform the reaction under ultrasonic activation as a modern confirmation of the proposed electron-transfer mechanism. We thank the referee for this suggestion and attempts to examine the results of this methodology are in progress. Ultrasonic irradiation produces switching of the reaction in some cases, and in the case of organolithium addition to arylcarbonyl compounds, some controversy exists about the mechanisms under sonication.[64]

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Supporting Information Available: NMR spectra of the irradiation of 1,3,5-triphenyl-4-penten-1-one, **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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