#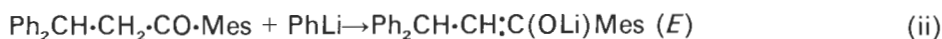 The Mechanisms of Stereoselective Michael Addition and Stereoselective Metallation yielding Z- and E-Lithio-3,3-Diphenylpropionylmesitylene
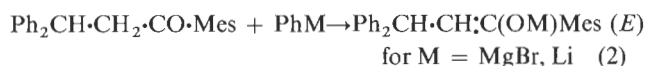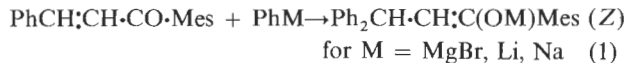
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Equilibration of the Z- and E-lithium enolate isomers of 3,3-diphenylpropionylmesitylene, obtained *via* reactions (i) and (ii), respectively, has shown a gradual change in the E:Z ratio with the cation-solvating

$$PhCH{:}CH{\cdot}CO{\cdot}Mes + PhLi \rightarrow Ph_2CH{\cdot}CH{:}C(OLi)Mes \ (Z) \qquad (i)$$

$$Ph_2CH{\cdot}CH_2{\cdot}CO{\cdot}Mes + PhLi \rightarrow Ph_2CH{\cdot}CH{:}C(OLi)Mes \ (E) \qquad (ii)$$

ability of the medium from 95:5 in ether to 18:32 in 1:1 ether–HMPT (hexamethylphosphoric triamide). The kinetic E:Z ratio of metallation (ii) decreases, though less sensitively, in the same direction. Michael addition (i) yields the Z isomer under kinetic control regardless of the cation-solvating ability of the medium. According to i.r. and n.m.r. data, cinnamoylmesitylene prefers the s-*trans* conformation, which would lead to the E isomer in a fast Michael reaction, fixing the conformational equilibrium in the initial state. The formation of the Z isomer *via* reaction (i) is accounted for by the steric demands of the attack of phenyl-lithium in the transition state. The role of the cation association to the oxygen atom is discussed with respect to the equilibrium and kinetic results.

Investigation into enolate stereochemistry began with the studies of Kohler *et al.*[1] and Nesmeyanov and his co-workers[2–4] on the *cis–trans* isomerism of magnesium and alkali metal enolates of 3,3-diphenylpropionylmesitylene. The case is remarkable for the highly stereoselective formation of one isomer *via* a Michael addition [equation (1)] and the other

$$PhCH{:}CH{\cdot}CO{\cdot}Mes + PhM \rightarrow Ph_2CH{\cdot}CH{:}C(OM)Mes \ (Z)$$
$$\text{for } M = MgBr, Li, Na \quad (1)$$

$$Ph_2CH{\cdot}CH_2{\cdot}CO{\cdot}Mes + PhM \rightarrow Ph_2CH{\cdot}CH{:}C(OM)Mes \ (E)$$
$$\text{for } M = MgBr, Li \quad (2)$$

isomer by metallation [equation (2)]. The respective configurations were assigned later.[5,6]

Nesmeyanov *et al.*[4] assumed a traditional representation of reaction (1) as a cyclic 1,4-addition (Scheme 1, path *a*), by which the Z configuration of the product was predicted. However, though many authors have tried to elucidate the mechanism of 1,4-addition of Grignard reagents to α-enones,[7–9] there is little evidence for a cyclic pathway in this type of reaction. To what extent the cyclic mechanism is valid for lithium and sodium reagents is another question. As seen in Scheme 1, the Z configuration of the Michael product is not ultimate proof of a cyclic addition. It denotes only a cisoid transition state, *i.e.* one which resembles the s-*cis* conformer of the initial ketone.

In this respect, it would be of interest to know to what extent Z-stereoselectivity is general for 1,4-addition and what kind of conditions are responsible for it. At this time there are few literature data available to answer these questions.

Compared with 1,4-addition, the steric result of metallation of carbonyl compounds has received greater attention. Nesmeyanov *et al.*[4] found that the isomer produced by reaction (2) was more stable than the product of (1) in the solid state. However, House,[10] who used Ph₃CM reagents (M = Li, K) in 1,2-dimethoxyethane (DME) in ketone metallation, found the Z isomers to be the more stable. This was expected, as the Z enolates provide a *trans*-orientation of the bulky hydrocarbon
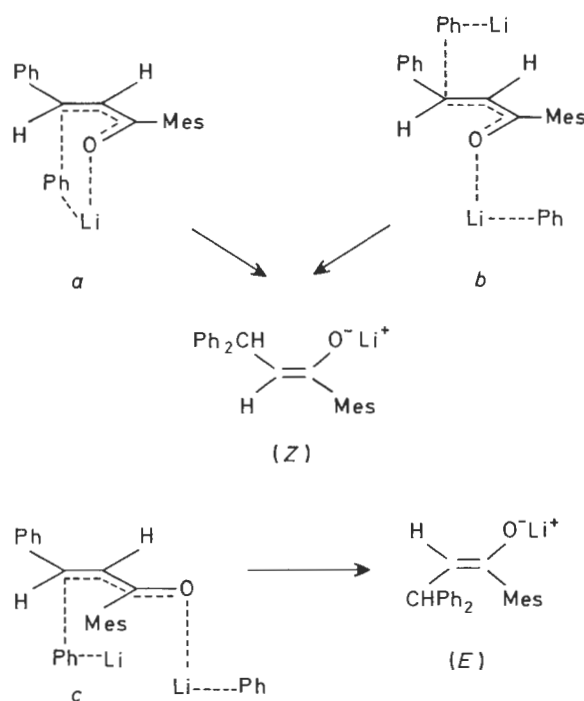
Scheme 1.

parts of the molecule. For that reason, the greater stability of the Z enolates has been generally recognised.[11]

Recent ketone metallation studies have been carried out with lithium amide bases in tetrahydrofuran (THF).[11–13] The formation of the E isomer under kinetic control has led Ireland *et al.*[12] to the assumption of a cyclic transition state of metallation with lithium in association with the carbonyl oxygen. In this model the steric demands of the proton-attacking amide particle are decisive for the configuration of the

Table 1. Equilibrium $E:Z$ ratio of lithio-3,3-diphenylpropionyl-mesitylene at room temperature in solution[a]

Entry	Solvent	Additive	Moles of additive per mol of PhLi	Enolate $E:Z$ molar ratio at equilibrium
1	Ether			$\geqslant 95:5$ [b,c]
2	Phenethole	TMEDA	1.5	$\geqslant 95:5$ [b,d]
3	THF			85:15
4	Ether	TMEDA	1.2	80:20
5	Ether	HMPT	2.0	70:30
6	DME			56:44 [c]
7	Ether	HMPT	6.0	47:53
8	Ether	HMPT[e]		18:82

[a] Unless otherwise indicated, equilibrium was reached *via* reaction (2). [b] Z Isomer practically undetectable. [c] Equilibrium reached *via* reactions (1) and (2). [d] Equilibrium reached only *via* reaction (1). [e] Ether and HMPT are mixed in equal volumes.

Table 2. Stereoselectivity of Michael addition (1) at room temperature under kinetic control

Entry	Solvent	Additive, mol per mol of PhLi	Kinetic enolate $E:Z$ molar ratio	Yield of enolate (%)	Protonation (%)	Unreacted ketone (%)
1	Ether		$\leqslant 5:95$ [a]	36	9	55
2	THF		$\leqslant 5:95$ [a]	44	5	51
3	DME[b]		7:93	90	5	5
4	Ether	TMEDA 1.0	5:95	68	19	13

[a] E Isomer practically undetectable. [b] Reaction performed with 2.4 mol of PhLi per mol of cinnamoylmesitylene.

product. In their metallation study of CH_3CH_2COR ketones, Heathcock *et al.*[11] also considered the volume of the attacking base to be responsible for the formation of the E-enolates. But, as the same authors observe a correlation between the volume of R and the $E:Z$ ratio in the product, they propose a less rigid, non-cyclic model of the transition state, in which the cation has no important role.

In the light of the above, it would be of interest to elucidate the mechanisms of the highly stereoselective reactions (1) and (2), and especially the role of cation association. This was apparently the basic idea of Nesmeyanov *et al.*[2-4] who investigated the respective MgBr, Li, Na, and $(CH_3)_4N$ enolates in non-polar solvents (ether and benzene). But their results are not readily interpretable since most of the enolates were obtained in heterogeneous conditions. We now report a study of the stereoselectivity of reactions (1) and (2) and the respective enolate equilibria in solution, with M = Li in media of varying solvating power.

Results and Discussion

Unless otherwise stated, reactions (1) and (2) were performed by adding a solution of cinnamoylmesitylene or 3,3-diphenyl-propionylmesitylene to a solution containing a slight excess of phenyl-lithium in the same solvent. The cation-solvating additive was introduced before the ketone when the product of kinetic control was to be studied. The reaction was quenched by adding acetyl chloride and the isomer ratio of the enolates was determined from ^1H n.m.r. spectra of their acetates in benzene.[6]

Equilibrium Studies.—The results of our equilibrium studies are presented in Table 1.

Consistent with observations for other alkali-metal enolates,[10,13] in the cases studied equilibration proceeded only in the presence of a carbonyl compound (3,3-diphenylpropionyl-mesitylene, accompanied in some cases by cinnamoylmesitylene). Except in the case of the experiments in ether, the amount of the saturated ketone gradually increased in the reaction mixture in spite of stringent avoidance of moisture. Most often the amount of the ketone was *ca.* 50 mol% in the organic residue of the samples acetylated at equilibrium. In DME, the amount of ketone varied from 25—80% in the equilibrium samples and this was not accompanied by any change in the equilibrium $E:Z$ ratio.

As seen in Table 1, the $E:Z$ equilibrium varies over a very wide range according to the solvent polarity and the eventual presence of cation-complexing additives. A high predominance of the E isomer is found in solvents of low polarity, while a gradual increase of the amount of the Z isomer is observed with increasing cation-solvating ability of the solvent system. In terms of the types of enolate ion pairs,[14] this seems to fit with a model in which a more tightly bound lithium cation with its outer solvating shell becomes more demanding sterically than the mesityl group, which has been noted to have a relatively small effective volume[11] in the enforced perpendicular position.[15] In recent years it has become increasingly apparent that lithium enolates exist as stable aggregates in ethereal solutions.[16-21] Seebach and his co-workers have obtained the X-ray structures of many lithium enolates which crystallise with solvent molecules,[17] and n.m.r. data have provided supporting evidence that similar structures are retained in solution.[19] Although we have no definite knowledge of the state of aggregation, a general picture of the effect of solvents and cation-solvating agents can be drawn along the lines outlined by Seebach.[18,20] In the Z isomer, the oxygen atom is flanked by the bulky mesityl and diphenylmethyl groups and will give rise to steric strains in tetramers with Li–O cubes or dimers with Li–O squares, which will make the E isomer more stable. With increasing solvating power of the solvent or in the presence of additives, the ratio enolate:solvent molecules in the aggregates will decrease and/or the enolate will move to an outer co-ordination position. In both cases, the position of the enolate will be sterically less demanding and consequently the E isomer less favoured. With the compounds studied, it takes six moles of HMPT in ether to make the juxtaposition of LiO to Ph_2CH slightly preferred to that of mesityl and the same preference is strongly increased in the 1:1 mixture of ether–HMPT.*

Recently a similar but much more modest dependence of the $E:Z$ equilibrium of the lithium enolates on addition of HMPT and TMEDA in THF solutions was observed.[13] The $E:Z$ ratio changes from 16:84 in THF to 6:94 in the presence of 4 equiv. of HMPT. This, and the general preference for the Z isomer (in contrast to the case of 3,3-diphenylpropionylmesitylene), supports the suggestion that, with the latter, the Z isomer is not favoured in aggregates with a high enolate content because of interference between the bulky groups of the enolate molecules. In the pentanone enolates, the methyl and ethyl groups are too small to interact in such a situation.

Michael Addition (1).—The results obtained on the Michael addition (1) are presented in Table 2. Considering the equilib-

rium data in Table 1, there is no doubt that the Z-selectivity of reaction (1) according to Table 2 is a kinetic result.

The most significant result from the experiments listed in Table 2 is that the high Z-selectivity is little affected by a more strongly cation-complexing solvent or the addition of TMEDA. This is in line with the observation of Nesmeyanov et al.[4] that the addition does not lose its stereoselectivity when phenyl-sodium is used instead of phenyl-lithium. Such behaviour is usually associated with the lack of an organising role of the metal, and has some parallel in the generally poor ul-lk selectivities[22] in reactions of enolates with enones.[23] This induced us to examine another possibility for the high selectivity; that is a fast reaction of phenyl-lithium fixing a preferred s-cis conformation of the initial enone, which is known to be the preferred conformation of the closely related chalcone.[24-27] Referring to the literature on chalcone, a comparative study of chalcone and cinnamoylmesitylene was undertaken. Our i.r. and n.m.r. results are shown in Tables 3 and 4, respectively. The high J values in Table 4 show that both ketones are in the E configuration.

As shown in Table 3, the i.r. spectrum of cinnamoylmesitylene is very different from that of chalcone with respect to relative band intensities. In solution, we have a weak s-cis carbonyl band of cinnamoylmesitylene for a strong one of chalcone and a strong s-trans carbonyl band of the former for a medium one of the latter. The difference is most dramatic in the solid state (Nujol), where cinnamoylmesitylene appears to be only s-trans and chalcone only s-cis. The ethylene stretching vibrations also provide evidence for a preferred s-trans conformation for cinnamoylmesitylene: the $C=C_{s-trans}$ band, which usually appears as an inflection of the much more intensive $C=C_{s-cis}$ band in compounds presenting both conformations,[25] is

observed as a separate band in the spectrum of cinnamoyl-mesitylene.

The s-trans character of cinnamoylmesitylene is consistent with the out-of-plane conformation of the mesityl group observed with other ketones.[15] In the studied case, the fixed out-of-plane conformation makes the mesityl group effectively small in the plane of the ethylene bond. The carbonyl bands of cinnamoylmesitylene are shifted to higher frequencies compared with chalcone, which supports the out-of-plane conformation of the mesityl group.

As seen in Table 4, the n.m.r. signals of the ethylene protons of cinnamoylmesitylene are considerably upfield in comparison with chalcone. This is readily accounted for by the shielding effect of the mesityl aromatic ring in a perpendicular position to the ethylene bond.[28] It is to be noted, however, that we did not observe with cinnamoylmesitylene a solvent-induced shift in benzene, as observed with other s-trans ketones.[27]

Thus the predominance of the s-trans conformation in the ground state of cinnamoylmesitylene excludes the possibility of conformationally determined Z-selectivity and the reason has to be sought in the steric demands of the transition state. The phenyl anion is a relatively large base and with the requirement of an attack more or less perpendicular to the conjugated system this would give rise to considerable steric hindrance by the protruding methyl groups of the mesityl moiety in the s-trans conformation leading to the E enolate. Whether the reaction occurs via a bridged or an open transition state as shown in Scheme 1 a and b, respectively, cannot be answered from the available evidence. The mesityl group suppresses 1,2-addition almost completely for steric reasons; the same interference will make a cyclic transition state from the s-trans conformation unfeasible. Recent experimental results on similar reactions[18,20] and theoretical studies of 1,2-additions of organolithium and organomagnesium compounds[29,30] strongly indicate that these proceed in the clusters found in solution. The latter outline a process beginning with co-ordination of carbonyl oxygen to the metal and proceeding by an early transition state where the Li-O bond is retained. The differences in geometry and orbital interactions between 1,2- and 1,4-additions render a comparison too speculative but we consider that the large β-C-O distance coupled with the observed weak solvent effect render a six-membered cyclic transition state unlikely.

Table 3. I.r. absorption bands of cinnamoylmesitylene (cin) and chalcone (ch)[a] relevant to the s-cis/s-trans ratio in both ketones, frequencies (ν) in cm⁻¹

Solvent	Compd.	ν_{C-H}, trans-out-of-plane vibr.		$\nu_{C=C}$ stretching vibr.		$\nu_{C=O}$ stretching vibr.	
		s-trans	s-cis	s-cis	s-trans	s-trans	s-cis
CCl₄	cin	980	988	1 609[b,c]	1 625m[c]	1 652s[c]	1 677w[c]
	ch	980 (sh)	990	1 611s[d]	d	1 650m[d]	1 669s[c]
CHCl₃	cin	985	995 (sh)	1 612[e]	1 629m	1 640s	1 670 (sh)
	ch	980	990	1 611s[d]	d	1 642m[d]	1 666s
f	cin	980		g	1 625m	1 644s	
h	ch	980 (sh)	990	1 607s[d]	d	d	1 665s

[a] Most used synonym of benzalacetophenone, PhCH:CHCOPh. [b] Superposition with aromatic absorption. [c] The reported result is close to that given in ref. 5. [d] The reported result is close to or coincides with that given in ref. 24. [e] Small peak on top of a broad aromatic band. [f] Solid state in Nujol. [g] A band at 1 612 cm⁻¹ of aromatic origin. [h] Solid state in a KBr disc.

Metallation (2) *of* 3,3-*Diphenylpropionylmesitylene.*—The metallation reaction (2) appears to be much more dependent on the cation-solvating ability of the medium than Michael addition (1). As seen in Table 5, the kinetic E-selectivity decreases with the increase of the cation-complexing ability of the solvent (ether < THF < DME). According to the results in Table 1, the equilibrium E:Z ratio is altered in the same direction. In ether and THF there is almost no difference between the kinetic and the equilibrium E:Z data. As the trace amounts of ketone found in the kinetic samples could not provoke considerable equilibration in the time elapsed between mixing of the reagents and quenching (see Experimental

Table 4. Proton n.m.r. chemical shifts (δ) and coupling constant of the ethylenic protons ($J_{\alpha,\beta}$/Hz) of cinnamoylmesitylene (cin) and chalcone (ch)

Solvent	Compd.	p-CH₃	o-CH₃	H_α[a]	H_β[a]	$C_6H_2(CH_3)_3$	Ph	$J_{\alpha,\beta}$
CDCl₃	cin	2.32	2.20	7.18	6.91	6.87	73.0—7.50	16.5
	ch[b]			7.44	7.78		7.32—7.69	15.5
C₆D₆	cin	2.15	2.20	7.21	6.94	6.71	6.95	16.5
	ch[b]			7.35	7.84		7.02—7.35	15.5

[a] The assignment of the signals of the ethylenic protons was based on the anisotropy effect of the carbonyl group[26] and the out-of-plane mesityl group.[28] [b] According to ref. 27.

Table 5. Stereoselectivity of metallation (2) at room temperature under kinetic control

Entry	Solvent	Additive mol per mol of PhLi	Kinetic enolate $E:Z$ molar ratio	Yield of enolate (%)	Protonation or non-reacted ketone (%)
1	Ether		92:8	95	5
2	THF		88:12	88	12
3	DME		85:15[a,b]	93	7
4	Ether	TMEDA 1.0	65:35	28	72

[a] Reaction performed with 2.4 mol of PhLi per mol of 3,3-diphenyl-propionylmesitylene; lower excess of PhLi produced lower yield of enolate and lower E-selectivity. [b] Higher $E:Z$ ratio was observed when the ketone solution was added to solid PhLi obtained after evaporation of ether.

section), the above kinetic data are reliable (within about 5% limits of error).

In DME, the yield of metallation and the $E:Z$ ratio in the kinetic samples depended on whether one or two equiv. of phenyl-lithium were used. As quantitative metallation required at least two equiv. of PhLi and also because the presence of free ketone could accelerate the equilibration process, already rather fast in DME, the kinetic result obtained with 2.4 equiv. of phenyl-lithium, as given in Table 5, was taken as most correct. In the case of DME, a clear difference between the equilibrium and the kinetic isomer ratio is observed. The E isomer, which is still the kinetic product (Table 5, entry 3), is no longer preferred at equilibrium (ca. 1:1 isomer ratio, Table 1, entry 6). The reverse is observed with ether–tetramethylethylenediamine (TMEDA), where the equilibrium $E:Z$ ratio is higher than the kinetic one (Table 1, entry 4 vs. Table 5, entry 4). As equilibration is very fast under the conditions of this experiment, the true kinetic $E:Z$ ratio may be still lower in this special case.

The sensitivity of the kinetic result of metallation to cation solvation suggests a special role of the cation in the transition state for metallation. The role of the cation is supported also by the observation that reaction (2) loses its stereoselectivity when lithium is replaced by sodium.[4]

Scheme 2 represents the presumed transition states leading to configuration Z (a, b) or E (c, d) based on oxygen–lithium co-ordination. The transition states leading to the Z isomer resemble a presumably favoured conformer of the initial ketone, in which the large diphenylmethyl group is eclipsed by the small carbonyl group. The transition states leading to the E isomer resemble the other conformer of 3,3-diphenylpropionylmesityl-ene, in which the large diphenylmethyl group is gauche to the mesityl group, an arrangement not likely to be favourable.

We have seen that the Z enolate loses its thermodynamic advantage in associating media and have accounted for it by an increase of the effective volume of the OLi group due most probably to aggregation. The transition state for metallation seems to be affected by similar phenomena. Association of the phenyl-lithium reagent to the carbonyl group[31] will increase the steric hindrance with the large diphenylmethyl group and favour the E enolate. If association to the carbonyl oxygen and the attack at the hydrogen atom are performed by one and the same phenyl-lithium molecule, the transition state is cyclic, as proposed by Ireland,[12] though an open model of the transition state does not exclude association between the carbonyl oxygen and phenyl-lithium and vice versa (Scheme 2, path c). In the studied case, the steric importance of the phenyl particle in the
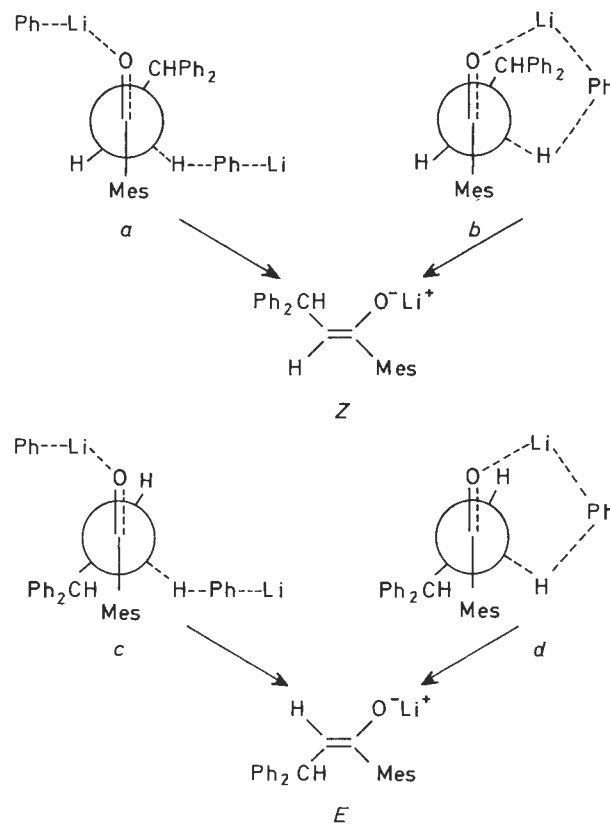
Scheme 2.

transition state for metallation is best demonstrated in DME, where the kinetic $E:Z$ ratio exceeds the thermodynamic one.

As already mentioned, there exists in the literature an attempt to interpret the E-stereoselectivity of metallation by the volume of the proton-extracting particle, independently of carbonyl–lithium association.[11] Though the decrease of the kinetic stereoselectivity in the ether–THF–DME range is an indication in favour of the role of the cation in the studied case, the most revealing experiment is that with TMEDA. One equiv. of this additive does not change strongly the isomer equilibrium in ether (Table 1, entry 4 compared with 1). TMEDA Is known to be a non-dissociating additive, which solvates externally the ion pairs[32] (which accounts also for the case in Table 1, entry 2). It has, however, a strong effect on the stereoselectivity of metallation (Table 5, entry 4 compared with 1), presumably by blocking the lithium cation and thus preventing the association of the reagent to the carbonyl group.

The results of our metallation study with phenyl-lithium indicate that the association of the lithium cation to the carbonyl group of the ketone is important for the stereoselective formation of the E enolate. The reported case brings support to the concept of cation-dependent steric results, of metallation of carbonyl compounds.

Experimental

Reagents and Solvents.—Reagent-grade commercially available reagents and solvents were used.

The ethereal solvents, previously dried and stored over sodium wire, were treated with LiAlH$_4$ and distilled under argon before use. Hexamethylphosphoric triamide was treated with CaH$_2$, vacuum-distilled, and stored over molecular sieve (4 Å). Tetramethylethylenediamine was boiled over NaOH, then over sodium, and distilled under argon. Phenyl-lithium[33] was

prepared and handled under argon. It was titrated acidimetrically in an excess of 0.1M-HCl before use. Cinnamoylmesitylene[3] was prepared by a Friedel–Crafts reaction of cinnamoyl chloride with mesitylene (m.p. 160—161 °C, lit., 163 °C). 3,3-Diphenylpropionylmesitylene[3] was prepared by addition of PhMgBr or PhLi to cinnamoylmesitylene and hydrolysis of the enolate obtained (m.p. 79—80 °C, lit., 82 °C).

Stereoselectivity of Reactions (1) *and* (2) *under Kinetic Control.*—Both reactions were performed under argon at room temperature as follows: 1.1—1.2 mol of PhLi (unless otherwise stated) per mol of the reaction ketone were transferred to the reaction flask and ether was replaced, after evaporation, by the chosen solvent, to which a cation-complexing additive (HMPT, TMEDA) was eventually added. The contents of the reaction flask were stirred for 5 min before the addition of cinnamoylmesitylene of 3,3-diphenylpropiomesitylene dissolved in the same solvent as PhLi. The total volume of the solvent corresponded to a 0.1M solution of the ketone. The reaction was performed under stirring and was quenched 5 min after the addition of the ketone with an excess of acetyl chloride, most often 0.2 ml CH₃COCl for 5 ml samples of the enolate solution. In the ether–TMEDA experiments (Table 2, entry 4 and Table 5, entry 4) the reaction was quenched 3 min after ketone addition. The crude acetylated product was taken in ether, water-washed, dried, evaporated, and dissolved in benzene for ¹H n.m.r. analysis.[6]

Equilibrium Studies.—Equilibration was most often performed *via* reaction (2) using 0.75 mol of PhLi per mol of 3,3-diphenylpropionylmesitylene. When equilibration was performed *via* reaction (1), one mol of PhLi per mol of cinnamoylmesitylene was used and 0.3 mol of 3,3-diphenylpropionylmesitylene were added as equilibrating agent in ether (Table 1, entry 1). Equilibration took about 24 h in ether and was faster with higher cation-solvating ability of the medium, in which case the gradual increase of the amount of the saturated ketone was also faster.

In an experiment *via* reaction (1) in DME, equilibrium ($E:Z = 53:47$) was reached in 90 min at 80 °C in the presence of 70 mol% of cinnamoylmesitylene and 5% of 3,3-diphenylpropionylmesitylene. A similar experiment *via* reaction (2) led in 45 min to equilibrium ($E:Z = 57:43$) in the presence of 25 mol% of 3,3-diphenylpropionylmesitylene.

The samples taken in appropriate time intervals during equilibration were treated as described for kinetic control studies.

Spectroscopic Studies.—*I.r. spectra.* The i.r. spectra of cinnamoylmesitylene and chalcone were taken on a UR 20, K. Zeiss Jena spectrophotometer on an extended scale calibrated against polystyrene.

N.m.r. spectra. The n.m.r. spectra of cinnamoylmesitylene were taken on a 100 MHz JEOL PS spectrometer using tetramethylsilane as standard.

The n.m.r. spectra of the acetylated samples were taken on a 60 MHz JEOL C 607 spectrometer. The product composition was estimated by integration of the signals of the *ortho* methyl protons in the mesityl moiety.[6]

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