

OBSERVATIONS ON THE EFFECT OF SILANES ON THE REACTION OF 10-METHYL- $\Delta^{1,9}$ -2-OCTALONE WITH LITHIUM DIMETHYLCUPRATE(I).

Steven H. Bertz

AT & T Bell Laboratories, Murray Hill, New Jersey 07974, U.S.A.

Robin A.J. Smith*

Department of Chemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

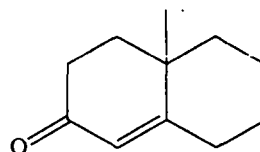
(Received in UK 20 March 1990)

ABSTRACT - The influence of silanes on the reaction of enones with cuprates has been examined using the title enone compound and $\text{Me}_2\text{CuLi.LiI}$. In ether solvent the effect of various silanes on the 1,4/1,2 addition ratio was minor. In tetrahydrofuran significantly increased 1,4/1,2 addition ratios and increased conversion of substrate was noted in the presence of silanes. Me_3SiCl proved to be the most effective of the silanes examined for preferential 1,4 enone addition.

Organometallic reagents based on copper have gained wide acceptance for use in organic synthesis.¹ In many respects they are unique reagents for carbon-carbon bond formation, particularly for conjugate addition to α,β -unsaturated ketones, and hence methodology to improve the overall efficiency and specificity of organocopper reagents is of current interest. Detailed knowledge of the mechanism of these reactions would obviously provide many avenues for improvement although the complicated equilibria exhibited by many of the common organocopper reagents and the dramatic change in reaction behaviour induced by modest solvent changes or small amounts of impurities creates a considerable experimental challenge. Recent spectroscopic observations^{2,3} of intermediates on the reaction pathway of organocuprate induced conjugate addition to α,β -unsaturated carbonyl compounds have provided some insight into the mechanism. Nonetheless, a complex, and in many areas, insufficiently characterized reaction scheme still remains despite considerable effort.

One area of development which has rapidly gained acceptance is the influence of silanes on the conjugate addition of organocopper reagents^{4,5}. Organocuprates are currently the most widely used type of organocopper reagent and, as most mechanistic information is available for these reagents, the research reported herein was limited to examination of silane effects on organocuprate reactions. Originally, chlorotrimethylsilane (Me_3SiCl) was added subsequent to the organocuprate conjugate addition reaction to trap the enolate produced from 1,4 addition as an enol silyl ether⁴. However the discovery⁵ that organocuprates and Me_3SiCl were compatible at low temperatures lead to the introduction of the silane to the organocuprate prior to the addition of the unsaturated substrate. Improved selectivity for 1,4 over 1,2 addition was noted with this protocol⁵ and also normally unreactive substrates were induced to undergo 1,4 addition^{4b}. This increased 1,4 selectivity, particularly in tetrahydrofuran (THF), which is normally not the solvent of choice for 1,4 addition with organocuprates⁶, led to the suggestion⁷ that Me_3SiCl is playing a more significant role in the overall reaction rate than simply trapping the enolate *in situ* as it is being created by an unassisted organocuprate 1,4 addition. As there appears to be no interaction between α,β -unsaturated carbonyl compounds and Me_3SiCl ⁵, the influence of the silane would appear to be on the organocuprate or some organocopper-alkene intermediate compound. The observed lack of formation of alkylated silanes and retention of organocuprate reactivity with acyl halides from a mixture of lithium dimethylcuprate and Me_3SiCl at temperatures where conjugate addition proceeds effectively indicated that the interaction of the silane with the organocuprate was not likely⁷. However there is spectroscopic evidence⁸ that some organocuprates do indeed interact with Me_3SiCl to produce modified organometallic species retaining cuprate reactivity. A mechanistic rationale has therefore been developed⁷ whereby the silane influence is effected at the $d-\pi^*$ cuprate-alkene stage by silicon-oxygen bond formation. This scheme implies the initial product in THF is an enol silyl ether and not an enolate. In ether solvent, using typical reaction conditions of 2-3 equiv of organocuprate, the addition of Et_3N or hexamethylphosphoramide (HMPA) is required^{4b} for effective isolation of the enol silyl ether of the 1,4 addition product.

Our recent observation² of a π -complex between lithium dimethylcuprate and 10-methyl- $\Delta^{1,9}$ -2-octalone (**1**), interest in the further unravelling the organocuprate mechanistic scheme, and a wish to increase the effectiveness of organocuprate reactions induced the study reported herein. We opted to use a combination of the most common, methyl substituted organocuprate together with **1**, whose cuprate chemistry has been well examined⁹, to investigate the silane effect. Coincidentally with our research in this area a report appeared¹⁰ detailing aspects of the conjugate addition reaction with silane activated cuprates using the relatively reactive lithium dibutylcuprate and a series of monocyclic and acyclic α,β -unsaturated aldehydes and ketones which are generally more reactive to organocuprate 1,4 addition than **1**.

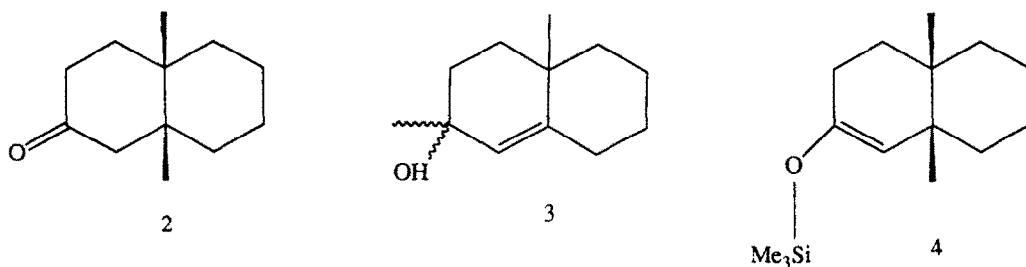


1

RESULTS AND DISCUSSION

Lithium dimethylcuprate was prepared from MeLi (2 equiv) and CuI at -30° to 0°C . Reactions were run on a 1

mmole scale at 0.1 M solution copper concentration. Although this cuprate has been shown to exist as a dimer¹¹ in some situations, the overall stoichiometry is such that one methyl group per copper is available for transfer to the substrate and hence the reagent is simply cited as $\text{Me}_2\text{CuLi}\cdot\text{LiI}$. Reactions of **1** with methyl organocuprate consisted of mixtures containing the 1,4 product **2**, the 1,2 product **3** (as a mixture of isomers) and the related silyl derivatives. The reaction product was analysed by vpc and vpc/ms comparison with purified materials. Reproducible analytical data was best obtained by treating the crude reaction mixture with aqueous acid. This process converted all of **3** into a mixture of three dienes (vpc/ms) whose peak areas were summed together to give the total amount of 1,2 product. The amount of enol silyl ether (**4**) was determined by vpc prior to acid treatment and related to the total amount of **2** obtained after acid hydrolysis. Due to the instability of the materials it was not possible to estimate the amount of silylation of the 1,2 product. In virtually all the reactions studied, the sum of the amounts of **1**, **2** and **3** was found to be $100 \pm 5\%$ of the amount of **1** initially used. For ease of comparison the results were standardized to 100%. Preliminary solvent studies showed that ether and dimethyl sulfide¹² gave comparable yields of 1,4 product (**2**) and similar response to the presence of silanes; however, reaction with THF was markedly different. This study was therefore focussed on reactions in ether and in THF. A summary of the results using Me_3SiCl is given in Table 1.



Mixing of **1** with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ in ether at -78°C gave a yellow solution of the π -complex², which after low temperature protonation returned only **1**. Increasing the temperature to 0°C resulted in a rapid reaction together with the production of a characteristic voluminous yellow methyl copper precipitate. Analysis of the product showed predominantly 1,4 addition (entry 1). Repetition of this reaction sequence with the addition of Me_3SiCl (1 equiv) 1 min prior to the addition of **1** gave a similar result (entry 2) except a modest amount of the total 1,4 product was silylated. Combination of **1** with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ in ether at -60°C allowed the reaction progress to be conveniently monitored over several hours. The results (Fig. 1) show that the reaction rate, as determined by the consumption of **1**, was only slightly increased in the presence of Me_3SiCl . Another feature of this reaction was the rapid initial production of the 1,2 product (**3**) in both reaction systems which then remained relatively constant as the 1,4 addition continued. The same behaviour was observed in our NMR study.² This may be related to a small concentration of free MeLi being available in the reaction solution, as MeLi reacts rapidly in a 1,2 sense with **1** in ether at -78°C . This difference in the rate of production of the 1,2 and 1,4 products was also demonstrated at 0°C by rapidly quenching (~ 3 sec) a reaction mixture even before the precipitation of methyl

TABLE 1 Reaction of 1 with Methyl Organocuprates (0.1 molar) in the Presence of Me₃SiCl^a

Entry	Solvent	Experiment ^b	Product ^c /%			1,4 Silylation ^d /%
			1	2	3	4/2
1	Ether	Me ₂ CuLi.LiI, -78°, 1, 60 min /0°, 30 min	>92 3	- 86	- 11	-
2	Ether	Me ₂ CuLi.LiI, -78°, Me ₃ SiCl 1 min /1, -78°, 60 min /0°, 30 min	>95 4	- 82	- 14	- 30
3	Ether	Me ₂ CuLi.LiI, 0°, 1, 4 sec	71	17	12	-
4	Ether	Me ₂ CuLi.LiI, 0°, 1 (0.5 equiv), 15 min /0°, Me ₃ SiCl, 30 min	1	92	7	74
5	THF	Me ₂ CuLi.LiI, -78°, 1, 60 min /0°, 30 min	87	3	10	-
6	THF	Me ₂ CuLi.LiI, 0°, 1 (0.5 equiv), 60 min	41	2	57	-
7	THF	Me ₂ CuLi.LiI, -78°, Me ₃ SiCl, 1 min /-78°, 1, 60 min	19	30	51	67
8	THF	Me ₂ CuLi.LiI, -78°, Me ₃ SiCl, 1 min /-78°, 1, 1 sec /-78°, 3.5 sec /-78°, 36 sec	88 36 23	4 22 31	8 41 46	81 75 73
9	THF	Me ₂ CuLi.LiI, -78°, 3 min /-78°, (1 + Me ₃ SiCl), 60 min	4	29	67	80
10	THF	Me ₂ CuLi.LiI, -78°, 3 min /-78°, 1, 3 min /-78°, Me ₃ SiCl, 60 min	-	28	73	82
11	THF	Me ₂ CuLi.LiI, 0°, 1, 1 min /0°, Me ₃ SiCl, 60 min	4	16	80	75
12	THF	Me ₂ CuLi.LiI, -78°, 30 min /-78°, 1, 3 min	75	0	25	-
13	THF	Me ₃ Cu ₂ Li, 0°, 1, 60 min	96	2	2	-
14	THF	Me ₃ Cu ₂ Li, 0°, 1, 1 min /0°, Me ₃ SiCl, 60 min	2	43	55	68
15	THF	Me ₃ Cu ₂ Li (0.5 equiv), 0°, (1 + Me ₃ SiCl), 60 min	42	24	34	8

^a all reactions were carried out using 1 mmole of each component unless stated otherwise.

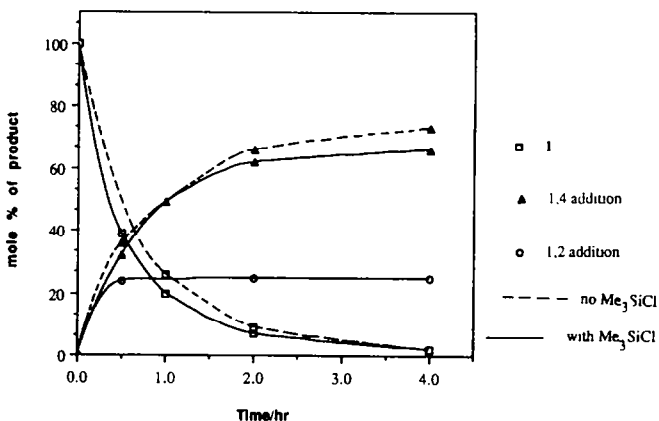
^b / indicates reagent addition or reaction sampling. i.e. entry 2 involved adding Me₃SiCl to the cuprate at -78° and 1 min later adding 1. Samples were taken after 60 min at -78° then after a further 30 min at 0°.

^c determined by vpc after acid treatment of the total reaction product.

^d the amount of 4 was determined by vpc of the reaction mixture prior to acid hydrolysis.

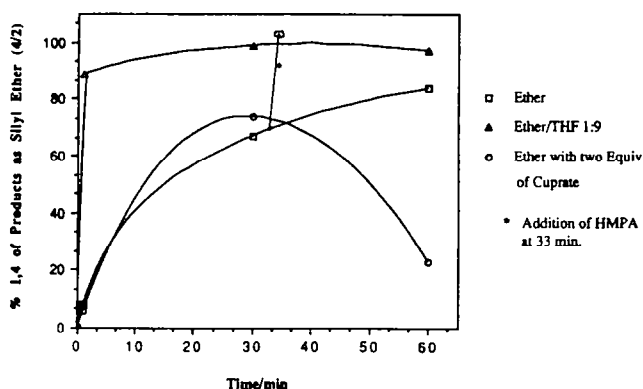
copper was evident (entry 3). The amount of 1,4 product present in the form of the silyl enol ether 4 increased with time, however the 1,4 addition was significantly more rapid than silyl ether formation. This feature was confirmed by performing an ethereal organocuprate mixture from **1** and $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ at 0°C followed by treatment with Me_3SiCl . After 1 hr, 84% of the 1,4 product was silylated (Fig. 2), whereas 1,4 addition was complete in seconds under the same reaction conditions.

Fig. 1. Reaction of **1** with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ in Ether at -60°C .



As noted previously^{4b}, the rate of production of **4** was significantly enhanced by adding HMPA (Fig. 2). This dramatic change is presumably the result of the base depolymerizing the organometallic cluster creating a less strongly coordinated and hence more nucleophilic enolate. In all of the experiments carried out to completion in ether solution (entries 1, 2, 4) the ratio of 1,4/1,2 product was relatively insensitive to temperature variation or the presence of Me_3SiCl . The rate of silylation of the 1,4 addition enolate was independent of the time between mixing **1** and $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ at 0°C and the subsequent addition of Me_3SiCl , indicating that any ageing effects were not altering enolate reactivity. Furthermore the order of mixing of the three components did not significantly alter the reaction rate or product composition.

Fig. 2. Silylation Rates of the 1,4 Addition Enolate with Me_3SiCl at 0°C .



Reaction of 0.5 equiv of **1** with ethereal $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ in the presence of Me_3SiCl showed slightly increased 1,4 selectivity (entry 4) to that obtained with 1:1:1 stoichiometry and a significantly increased amount of enol silyl ether formation. However the percentage of silylated material was found to change with time in this reaction medium containing excess cuprate (Fig. 2) and was significantly depleted after 60 min. A similar variation of silylation with time was noted with an π -complex mixture which was allowed to "age" at -78°C for 60 min prior to the addition of Me_3SiCl at 0°C . Hence the common practical observation of low returns of enol silyl ether with organocuprates (2-3 equiv) in ether solvents can be explained as a combination of inhibited enolate reactivity due to oligomeric cluster formation and the instability of the silyl ether product towards the usual reaction environment. Silyl enol ethers can be satisfactorily produced in an ethereal environment by using equimolar

stoichiometry and allowing sufficient time for the reaction.

In summary the influence of Me_3SiCl on the conjugate reactivity of $\text{Me}_2\text{CuLi.LiI}$ in ether would appear to be of a very minor nature and in practical terms offer no synthetic advantage. The unsuitability of ether as a solvent for silane activation of cuprates was also noted with dibutylcuprate¹⁰ and commented upon⁵ in an early landmark paper in this area.

Reaction of **1** with $\text{Me}_2\text{CuLi.LiI}$ in THF gave very different results. In the absence of silane little reaction occurs at -78°C while at 0°C only modest amounts of addition products are formed (entry 5). Reaction with 2 equivalents of $\text{Me}_2\text{CuLi.LiI}$ increased the amount of 1,2 product (entry 6). However, introduction of Me_3SiCl to $\text{Me}_2\text{CuLi.LiI}$ in THF at -78°C followed by **1** induced a rapid reaction (entry 7). Sampling after 60 min showed that the product was predominantly the 1,2 product **3**, as noted previously⁵. The product composition was unchanged after longer reaction times or at higher subsequent temperatures (0°C). The majority of the 1,4 product was obtained as the silyl enol ether **4**. Repetition of this reaction with sampling at short intervals after the addition of **1** showed that, in contrast to the reaction in ether, the 1,2/1,4 product ratio was reasonably constant during the course of the reaction (entry 8). Also apparent from this experiment was the fact that significant amounts of the silylated 1,4 product were formed even in the initial stages of the reaction. These data are consistent with the concept of the 1,4 and 1,2 products being produced by silane-induced partition of a common intermediate. Premixing of **1** and Me_3SiCl before addition to the cuprate gave comparable results (entry 9) with a higher overall chemical conversion of **1**. This increased conversion could reflect some partial deactivation or decomposition of the cuprate reagent on mixing with Me_3SiCl even after 1 min at -78°C . The observation of the high preponderance of silylated 1,4 product in these THF reactions prompted an examination of the rate of reaction of the enolate organocopper mixture with Me_3SiCl in THF. It was found that the enolate, produced from **1** and $\text{Me}_2\text{CuLi.LiI}$ in concentrated ether solution, was rapidly silylated in 1:9 ether/THF at 0°C (Fig. 2). At -78°C , under the same reaction conditions, the enolate was *ca* 15% silylated after only 4 sec exposure to Me_3SiCl added subsequently. This result indicates that silane activation of conjugate addition in THF could possibly occur before enolate formation and be followed by the demonstrated rapid silylation or more likely O-silylation is the essential promotional step in the overall mechanism.

Addition of **1** to $\text{Me}_2\text{CuLi.LiI}$ in THF at -78°C gives a yellow solution presumably containing π -complexes similar to those observed² in ether. Subsequent treatment of this solution with Me_3SiCl gave a comparable mix of products (entry 10) to that observed by premixing **1** and silane (entry 9). A similar reaction at 0°C gave also showed little variation of product composition (entry 11). As with the ether reactions some loss of silyl ether was noted over a period of time in some cases. These usually involved lengthy reactions of **1** and cuprate at -78°C prior to silane addition or when the reaction was allowed to warm to 0°C before completion. Despite these variations the overall 1:4/1:2 ratio remained constant.

If a 0.1 molar THF solution of $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ is held at -78°C for ~ 15 min a white precipitate is slowly formed. This material could be MeLi , as addition of **1** to this mixture gives only 1,2 addition (entry 12). The formation of $\text{Me}_3\text{Cu}_2\text{Li}$ in THF solution is well established¹³ and consideration was given to the involvement of this cuprate in these reactions *via*:



Substrate **1** was essentially unreactive towards $\text{Me}_3\text{Cu}_2\text{Li}$ (entry 13) however introduction of Me_3SiCl to this mixture resulted in a rapid reaction and the highest 1:4/1:2 ratio with THF observed in this study was obtained (entry 14). Reaction of **1** with 0.5 equiv of $\text{Me}_3\text{Cu}_2\text{Li}$ (entry 15) indicated only one methyl group per cuprate unit was available for transfer but the high 1:4/1:2 ratio was retained.

These studies in THF served to confirm the remarkable activating effect of Me_3SiCl on organocuprate reactivity. Most reports of silane modified organocuprate reactions have used Me_3SiCl as the silicon source. However the compatibility of lithium dimethylcuprate in THF with *t*- $\text{BuMe}_2\text{SiOTf}$ and *i*- Pr_3SiOTf at -78°C has been established⁵ and the activation of organocopper (RCu) reagents towards conjugate addition with Me_3SiCl and also Me_3SiI has recently been reported.^{46,14} We therefore undertook a survey of the effect of a range of organosilanes on the reaction of **1** with $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ and the results are presented in Table 2. The π -complex was preformed at -78°C followed by silane addition in a standardized reaction sequence in order to minimize any decomposition from direct reaction between the organometallic reagent and the silane.

In ether the highest 1,4/1,2 ratio was observed using Me_3SiCl , and a regular decrease was noted down the halogen series. The more reactive silylating agents (-CN, -OTf, -I) gave virtually complete 1,4 silylation whereas the less reactive halides (-Br, -Cl) produced lower silylation levels, attesting again to the unreactive nature of the 1,4 enolate in ether solution. The results with Me_3SiCN were very similar to those obtained from Me_3SiCl and the cuprate produced from $2\text{MeLi} + \text{CuCN}$. This indicates that possibly the same reagent is present in both reactions implying ligand exchange between silicon and copper.

The results obtained in THF solvent clearly show that the silane enhanced reactivity of organocuprates is not confined to Me_3SiCl although it did produce the highest 1,4/1,2 ratio. Interestingly, the reactive halosilanes (Me_3SiBr , Me_3SiI) did not produce any 1,4 silylation product under these reaction conditions. The $\text{Me}_3\text{SiCN} + \text{Me}_2\text{CuLi}\cdot\text{LiI}$ combination seemed to be again comparable as regards reactivity to the $\text{Me}_3\text{SiCl} + (2\text{MeLi} + \text{CuCN})$ system and the conversion efficiency of this mixture was much advanced over the comparable reaction in ether.

Having established the superiority of the chlorosilane a brief study was made of the variation of the organic ligands. Reaction in the presence of Ph_2MeSiCl was slower than with Me_3SiCl and the 1,4/1,2 ratio was not encouraging. Reaction with *t*- BuMe_2SiCl was even slower and much unreacted **1** was recovered. The inability

of $t\text{-BuMe}_2\text{SiCl}$ to facilitate conjugate addition has also been noted with more reactive cuprates¹⁰. Addition of HMPA or related compounds to $t\text{-BuMe}_2\text{SiCl}$ was required to obtain activity comparable to that of Me_2SiCl alone¹⁰.

TABLE 2 Reaction of 1 with $\text{Me}_2\text{CuLi.LiI}$ in the Presence of Various Silanes

		-78°		[Si] 1 equiv	0°	
1 + $\text{Me}_2\text{CuLi.LiI}$		→		→	→	product
		6 min		-78°, 6 min	6 min	
Solvent: Ether						
[Si]	Product ^a /%			1,4 Silylation ^b /%		
	1	2	3		4/2	
none	3	86	11	-		
Me_3SiCl	3	79	18	11		
Me_2SiBr	1	62	37	59		
Me_3SiI	0	57	43	94		
Me_2SiCN	65	16	19	97		
$\text{Me}_3\text{SiOTf}^c$	13	30	57	96		
$\text{Me}_2\text{SiCl/CuCN}^d$	57	17	26	97		
Solvent: THF						
none	87	3	10	-		
Me_3SiCl	1	36	63	21		
Me_2SiBr	0	31	69	0		
Me_3SiI	0	16	84	0		
Me_2SiCN	0	28	72	87		
$\text{Me}_3\text{SiOTf}^c$	0	20	80	19		
$\text{Me}_2\text{SiCl/CuCN}^d$	0	27	73	86		
$t\text{-BuMe}_2\text{SiCl}$	55	5	40	*		
Ph_2MeSiCl	4	24	72	*		

^a determined by vpc after acid hydrolysis.

^b determined by vpc prior to acid hydrolysis.

^c reaction at -78° for 6 min only.

^d prepared from 2 MeLi + CuCN followed by Me_2SiCl (1 equiv).

* amount of silylation not determined.

Me_3SiOTf was examined to evaluate the effect of a strongly Lewis acidic silyl species on the reaction. This silane reacted with $\text{Me}_2\text{CuLi.LiI}$ even at -78°C (~70% consumed after 5 min) so the reactions were not allowed to warm above this temperature. Reaction with the π -complex in ether at -78°C proceeded rapidly to give a product mixture with similar composition to that obtained from Me_3SiCl in THF (Table 1, entry 2). High 1,4 silylation was noted and it would appear that, unlike the halosilanes, Me_3SiOTf is sufficiently reactive to induce collapse of the π -complex in ether at -78°C presumably by O-silylation. Me_3SiOTf in THF showed no special reaction characteristics.

CONCLUSION

It is worthy of note that **1** is a sterically and electronically demanding α,β -unsaturated ketone towards organocuprate conjugate addition. Most unsaturated ketone substrates would be expected to react with greater 1,4 selectivity than **1**. A study of this nature with **1** places therefore substantial selectivity demands on the organometallic reagent and hence results such as Table 1, entry 14 are particularly significant for synthetic application if it is necessary to operate in THF. Me_3SiCl , the most common electrophilic silylating agent, proved most effective at activating $\text{Me}_2\text{CuLi.LiI}$ in THF.

The detailed rationale of this reactivity enhancement remains elusive. Any explanation for this phenomenon must account for the preponderant production of the silylated 1,4 addition product and the evolution of the 1,4 and 1,2 products from a common intermediate. These features are consistent with current mechanistic proposals⁷ although explanation of 1,4/1,2 selectivity would appear to require further mechanistic development. The possible intermediacy of more complex organocuprate species such as $\text{Me}_3\text{Cu}_2\text{Li}$ and/or transient silyl modified cuprates cannot be discounted given the current levels of knowledge in this area.

EXPERIMENTAL

All experiments were carried out in septum capped vials using CuI and MeLi as described previously¹². 10-Methyl- $\Delta^{1,9}$ -2-octalone (**1**) was prepared by literature methods¹⁵ or obtained commercially (Aldrich). The 1,4 products, **2** and **4**, were isolated from reaction mixtures for identification and to obtain vpc parameters. The 1,2 product, **3**, was obtained as a sensitive mixture from the addition of MeLi to **1** in ether.

Analysis of the reaction mixtures was carried out on a Hewlett Packard Model 5880 gas chromatograph, fitted with a 50m x 0.2 mm SE-30 fused silica capillary column. The chromatography output was integrated on a Hewlett-Packard integrator. The column temperature was programmed to run from 40°C to 250°C at 10°/min. Under these conditions the retention times for **1**, **2**, **3** [derived diene mixture] and **4** were 20.15, 20.41 [16.40, 17.10, 17.20] and 12.14 min respectively. The internal standard was dodecane (37.6 ± 0.2 mg, retention time 15.81 min) and on this basis the response factors for **1**, **2**, **3** (dienes) and **4** were 1.30, 1.27, 1.04 and 1.32. All silanes were obtained from commercial sources (Aldrich) and were used as received.

Typical Procedures:

(a) $\text{Me}_2\text{CuLi.LiI}$, Me_3SiCl , ether (Table 1, entry 2)

In an argon-filled dry box CuI (190.6 mg) and a magnetic stir-bar was placed in a 4-dram vial which was then sealed with a septum. The vial was removed from the dry box, connected to a static nitrogen atmosphere with a syringe needle and dry ether (6.0 ml) was added. The vial was then cooled to 0°C and ethereal MeLi (1.4 ml, 1.43 M, 2.0 mmole) was added with stirring. After 6 min the clear colourless solution was cooled to -78°C and Me_3SiCl (130 μl) added followed 1 min later by a mixture of **1** (167.8 mg) and dodecane (37.5 mg) in ether (3.0 ml) to produce a brown solution. After 1 hour at -78°C a sample (~ 1 ml) was removed with a syringe precooled to -78°C and added to nitrogen sparged aqueous NH_4Cl (5 ml, 3 M). The mixture was shaken at room temperature and the organic layer separated, dried (MgSO_4) and analysed by vpc to show only **1** (>160 mg).

The remainder of the reaction solution was warmed to 0°C for 30 min then worked up by addition of aqueous NH_4Cl . Analysis of the dry ethereal extract showed **1** (6.7 mg) and **4** (62.0 mg). The sample was then treated with an equal volume of 1:9 10% aqueous $\text{H}_2\text{SO}_4/\text{THF}$ at room temperature for 1 hour then dried (MgSO_4) and analysed to give **1** (6.1 mg), **2** (147.6 mg) and **3** as the sum of three vpc peaks (23.1 mg).

(b) $\text{Me}_2\text{CuLi.LiI}$, Me_3SiCl , THF (Table 1, entry 7)

Ethereal MeLi (1.20 ml, 1.54 M, 2.0 mmol) was added to a stirred suspension of CuI (190.2 mg) in dry THF (6 ml) at 0°C. After 6 min at 0°C the clear solution was cooled to -78°C and 2 min later Me_3SiCl (130

- μl) was added. After 1 min a mixture of **1** (163.5 mg) and dodecane (37.4 mg) in dry THF (3 ml) was added to give a yellow solution containing a small amount of white precipitate. After stirring 1 hr at -78°C the reaction was sampled as in (a). Analysis of the product showed **4** (48.1 mg). Treatment of the product with aqueous H_2SO_4 as in (a) followed by analysis showed **1** (31.8 mg), **2** (52.4 mg) and **3** (82.4 mg).
- (c) $\text{Me}_3\text{Cu}_2\text{Li}$, Me_3SiCl , THF (Table 1, entry 14).
Ethereal MeLi (0.9 ml, 1.65 M, 1.49 mmol) was added to a stirred suspension of CuI (190.7 mg) in dry THF (6 ml) at -30°C . After 6 min the clear solution was warmed to 0°C and Me_3SiCl (130 μl) added. After 1 min a solution of **1** (82.4 mg) and dodecane (19.1 mg) in dry THF (3 ml) was added producing a yellow precipitate. After 1 hour at 0°C sampling as in (a) gave **4** (38.0 mg). Acid treatment as in (a) followed by vpc analysis showed **1** (1.4 mg), **2** (38.9 mg) and **3** (45.9 mg).
- (d) Me_2CuLiLi , Me_3SiI , ether
Ethereal MeLi (1.4 ml, 1.43 M, 2.0 mmol) was added to a mixture of CuI (190.3 mg) and dodecane (37.4 mg) in dry ether (9 ml) at 0°C . After 6 min the clear solution was cooled to -78°C . After 6 min **1** (162.9 mg) was added neat which immediately resulted in a yellow brown solution. After a further 6 min at -78°C Me_3SiI (145 μl) was added to give an orange solution. After 6 min at -78°C the mixture was allowed to warm to 0°C for 6 min. A yellow precipitate was produced at this stage. Sampling as in (a) showed **4** (135.2 mg). Acid treatment as in (a) followed by vpc analysis gave **2** (70.0 mg) and **3** (101.7 mg).
- (e) 2MeLi , CuCN , Me_2SiCl , THF
MeLi (1.4 ml, 1.43 M, 2.0 mmol) was added to a suspension of CuCN (89.2 mg) and dodecane (37.6 mg) in dry THF (9 ml) at 0°C . After 6 min the clear solution was cooled to -78°C and **1** (163.2 mg) was added after a further 6 min producing a pale yellow solution. After a further 6 min at -78°C , Me_2SiCl (130 μl) was added producing some lightening of the solution colour. After 6 min at -78°C the reaction was warmed to 0°C for 6 min. The very yellow pale yellow solution which resulted was worked up as for (d) to give **2** (48.1 mg), including **4** (57.7 mg), and **3** (116.4 mg).

ACKNOWLEDGEMENTS

This research has been assisted (in part) by grants from the Research Committees of the University of Otago and the New Zealand Universities Grants Committee.

REFERENCES

- Recent reviews: (a) Taylor, R.J.K. *Synthesis*, **1985**, 364; (b) Lipshutz, B.H., *Synthesis*, **1987**, 325; (c) Normant, J.F. and Alexakis, A. *Current Trends in Organic Synthesis*, Pergamon Press, New York **1983**, 291; (d) Carruthers, W. *Comprehensive Organometallic Chemistry*, **1982**, 7, 661; (e) Posner, G.H. *Organic Reactions*, **1972**, 19, 1.
- Bertz, S.H. and Smith R.A.J. *J. Amer. Chem. Soc.*, **1989**, 111, 8276.
- Christenson, B., Olsson, T. and Ullenius, C. *Tetrahedron*, **1989**, 45, 523.
- (a) Chuit, C., Foulon, J.P. and Normant, J.F. *Tetrahedron*, **1981**, 37, 1385; (b) Alexakis, A., Berlan, J. and Besace, Y. *Tetrahedron Lett.* **1986**, 27, 1047; (c) Nakamura, E., Matsuzawa, S., Horiguchi, Y. and Kuwajima, I. *Tetrahedron Lett.*, **1986**, 27, 4029; (d) Johnson, C.R. and Marren, T.J. *Tetrahedron Lett.*, **1987**, 28, 27; (e) Bergdahl, M., Lindstedt, E.-L., Nilsson, M. and Olsson, T. *Tetrahedron Lett.*, **1988**, 44, 2055.
- Corey, E.J. and Boaz, N.W. *Tetrahedron Lett.*, **1985**, 26, 6019.
- House, H.O. and Wilkins, J.M. *J. Org. Chem.*, **1978**, 43, 2443.
- Corey, E.J. and Boaz, N.W. *Tetrahedron Lett.*, **1985**, 26, 6015.
- Lindstedt, E.-L., Nilsson, M. and Olsson, T., *J. Organometal. Chem.*, **1987**, 334, 255.
- (a) Smith, R.A.J. and Hannah, D.J. *Tetrahedron*, **1979**, 35, 1183; (b) Hannah, D.J., Smith, R.A.J., Teoh, I. and Weavers R.T., *Aust. J. Chem.*, **1981**, 34, 181; (c) Smith, R.A.J. and Vellekoop, A.S. *Tetrahedron*, **1989**, 45, 517.
- Matsuzawa, S., Horiguchi, Y., Nakamura, E., and Kuwajima, I. *Tetrahedron*, **1989**, 45, 349.
- Pearson, R.G. and Gregory, C.D. *J. Amer. Chem. Soc.*, **1976**, 98, 4098.
- Bertz, S.H. and Dabbagh, G. *Tetrahedron*, **1989**, 45, 425.
- Ashby, E.C. and Watkins, J.J. *J. Amer. Chem. Soc.*, **1977**, 99, 5312.
- Bergdahl, M., Lindstedt, E.-L., Nilsson, M. and Olsson, T. *Tetrahedron*, **1989**, 45, 535.
- Heathcock, C.H., Ellis, J.E., McMurry, J.E. and Coppoline, A., *Tetrahedron Lett.*, **1971**, 4995.