Unusual Regiochemical Control of the Reactivity of Some Organometallics with Chalcone

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A series of α-thio- and seleno-alkyl-lithiums add to chalcone mainly at the C-3 site in tetrahydrofuran (THF) and quite exclusively at its C-1 site in THF–hexamethylphosphoric triamide; these results contrast with those previously described for other enals and enones.

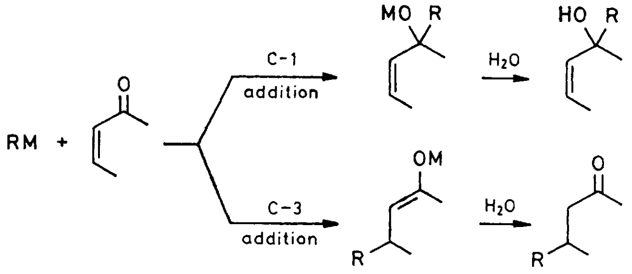
The regiochemical control of the reactivity of organometallics towards α-enones has been the subject of intensive and constant research since 1887.[1,2]

It has been observed that whether attack occurs at C-1 or C-3 (Scheme 1) is highly dependent upon the structure of the two reagents.[2] More recently however, it was discovered that

Table 1. Reaction of chalcone with various organometallics (**1a**—**g**).

					THF		THF–HMPT	
	X	R^1	R^2	R^3	(3)/(4) ratio	Overall yield (%)	(3)/(4) ratio	Overall yield (%)
(**1a**)[a]	S	Ph	Pr^i	Me	2/98	81	85/15	54
(**1b**)[b]	S	Me	SMe	Me	5/95	75	95/5	79
(**1c**)[a]	S	Ph	SPh	H	95/5	91	95/5	89
(**1d**)[b]	S	Ph	SPh	Me	26/74	82	83/17	84
(**1e**)[b]	S	—$[CH_2]_3$-S-		H	50/50	78	95/5	74
(**1f**)[b]	Se	Me	SeMe	Me	25/75	91	95/5	77
(**1g**)[b]	Se	Ph	SePh	Me	55/45	60	98/2	63

[a] Ratio of (**3**) to (**4**) determined from analytically pure (**3**) and (**4**) separated by preparative layer chromatography (SiO_2). [b] Ratio of (**3**) to (**4**) determined by ^1H n.m.r. spectroscopy.



Scheme 1

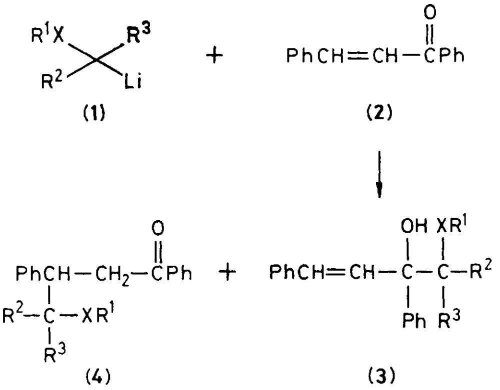
the experimental conditions also play a crucial role in the control of such reactions.[2]

We have reported that, in tetrahydrofuran (THF) and at −78 °C, α-lithiosulphides[3] and 1,1-bisthioalkyl-lithiums[4] and their seleno-analogues[4,5] react with various enals[4b] and cyclic and open-chain enones[3,4] to give products resulting mainly from attack at C-1 (condition A). We also reported[2] that the presence of hexamethylphosphoric triamide in the reaction medium (condition B) dramatically changes the course of the reaction, allowing in several instances the introduction of the organometallic reagent predominantly or exclusively at the C-3 site of these enones. Both types of reaction were found to be kinetically controlled.[3,4] This notable effect of HMPT on the reaction was simultaneously observed by Brown[6] and by Seyden-Penne[3] and has since been efficiently exploited.[7]

We report herein the results of our study of chalcone, a special case since chalcone is known to react readily with various organometallics in THF or ether mainly at the C-3 position. This has been observed with a variety of organometallics including α-lithionitrosamines,[8] α-lithio-sulphides[3] and -selenides,[5] α-lithiodithioacetal *S*-oxides,[7b] some phosphorus ylides,[9] α-lithiophenylacetonitrile,[11] and α-potassiophosphonates.[11] This behaviour has been correlated by House[12] with the particularly high half-wave potential of its electrolytic reduction and by Seyden-Penne[10,11] with the particularly low level of its LUMO.

In accord with these observations and in contrast with the case of other enones,[3,4] we found that α-lithiosulphides (**1a**), 1,1-bisthioalkyl-lithiums (**1b**—**e**), and their seleno-analogues (**1f,g**) react with chalcone (**2**) in THF (condition A) to produce a mixture of C-1 and C-3 adducts (**3**) and (**4**) in which the latter often predominate (Scheme 2). We therefore decided, with our previous work in mind, to perform the reaction in the presence of HMPT to allow the complete production of the C-3 adduct (**4**).

We were rather surprised to find, however, that instead C-1 attack was highly favoured under these experimental conditions† and the alcohols (**3**) were the main products (Scheme 2, Table 1).



Scheme 2

Table 2. Results under various conditions for (**1d**) (R^1 = Ph, R^2 = SPh, R^3 = Me, X = S).

Conditions	(3)/(4) ratio[a]	Overall yield (%)
THF	26/74	82
DME	63/27	74
THF–Kryptofix-2,2,2 (1 equiv.)	70/30	76
THF–HMPT (1 equiv.)	83/17	84

[a] Ratio determined by ^1H n.m.r. spectroscopy.

We have carefully checked, in the specific case of (**1f**), that the reaction occurs under kinetic control. Addition of HMPT (2.5 equiv.) to a THF solution containing the enolate and a small amount of the alcoholate from (**1f**) and chalcone (condition A), does not change their initial ratio whether the reaction is conducted at −78 °C or at higher temperatures (0 °C or 20 °C).

This reversed reactivity was also found when the reactions were performed at −78 °C in THF in the presence of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan (Kryptofix-2,2,2 from Merck),[4a] and in dimethoxyethane

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† The lithio-derivative of acetaldehyde cyanohydrin prepared according to Stork (G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, 1971, **93**, 5286) reacts mainly at the chalcone C-1 site in THF (C-1/C-3 = 82/18). This ratio is almost identical if the reaction is performed in THF–HMPT (C-1/C-3 = 85/15). These results contrast with those reported by Seyden-Penne[7c] involving the reaction of the same organometallic with cyclohexenone.

(DME),[4] under conditions known[4] to favour the C-3 addition of the organometallics **(1f)** with various cyclenones. Table 2 gives the results for **(1d)**.

No results related to ours have, to our knowledge, been reported to date‡ or even theoretically expected.

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‡ Hünig has also described (S. Hünig and G. Wehner, *Chem. Ber.*, 1980, **113**, 302) that HMPT favours the C-1 addition of lithium derivatives of silylated benzaldehyde cyanohydrins to various enones. These results, however, do not seem to be related to ours since no difference of regioselectivity has been observed between chalcone (unpublished results from our laboratory) and other enones.