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Diethyl Lithiomaleate: Preparation and Use in Synthesis.

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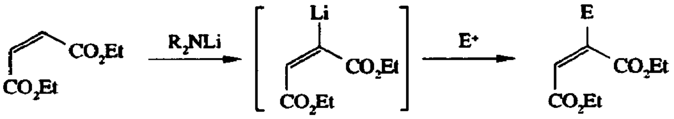
Abstract : The paper describes a simple method for the generation and alkylation of diethyl lithiomaleate. These reactions proceed with complete retention of alkene geometry, providing a convenient method for the diastereoselective introduction of this useful four carbon synthon.

The ability of many heteroatoms to facilitate the deprotonation of neighbouring unsaturated carbon centres has inspired much current interest.[2] An attractive aspect of this chemistry is that alkenyl anions, unlike their radical counterparts, are configurationally stable making them particularly useful in synthetic endeavours.[3] As part of some ongoing studies towards the podophyllin lignans, we had cause to desire a synthon for the diethyl maleate anion. Clearly the most attractive and strategically the simplest method to achieve this aim was to effect the direct deprotonation of diethyl maleate (Scheme).[4] In this *letter* we wish to report our realisation of that objective and highlight the ease with which this method may be employed for the diastereoselective introduction of this highly functionalised four carbon fragment.

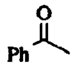
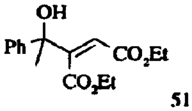
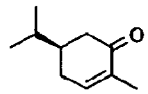
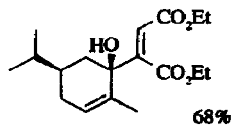
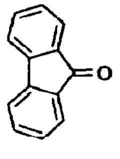
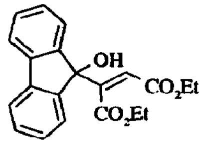
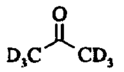
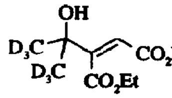
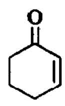
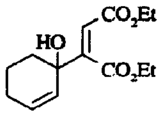
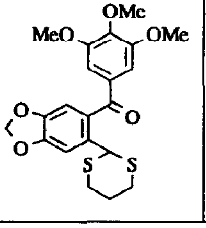
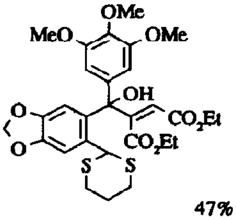


Scheme

Our favoured method to accomplish this transformation is to add diethyl maleate (5 mmol) to a cooled (-78°C) solution of *N*-lithio-2,2,6,6-tetramethylpiperidine (5 mmol) in THF and then immediately quench the partially formed anion with a trap (2 mmol). In this way the desired adducts may be formed in good to moderate yield (Table). The use of LDA or LiHMDS was found to be less satisfactory under all conditions explored.

In each of the cases studied the reaction was found to be highly selective and proceeded well with both simple and complex substrates, *e.g.* the podophyllin precursor (Table entry F).[5] No isomerisation of the alkene was observed. With α,β-unsaturated ketones the product of 1,2-addition was formed exclusively, for (*R*)-carvone providing the adduct as a single enantiomer in 68% yield (Table entry D). Despite of the use of excess of base, yields were not diminished with enolisable ketones.

Table: Coupling Reactions of Diethyl Lithiomaleate with Ketones.

	Electrophile	Adduct and Yield		Electrophile	Adduct and Yield
A		 51%	D		 68%
B		 58%	E		 54%
C		 63%	F		 47%

The reaction was less satisfactory with aldehydes. For example, when 3,4,5-trimethoxybenzaldehyde was used in this sequence the adduct was provided in *c.a.* 30% yield, together with copious quantities of 3,4,5-trimethoxybenzyl alcohol. We are presently investigating a number of extensions of this methodology and it's application in target orientated synthesis.

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