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A SELECTIVE, ALLYLIC CROSS-COUPLING REACTION. THE GENERATION OF ALLYLLITHIUM REAGENTS BY REDUCTION OF ALLYL MESITOATES.

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The coupling of two allylic units is in essence a very direct route to the 1,5-diene system found in numerous naturally occurring linear isoprenoid compounds, but in practice this approach is fraught with many difficulties. The classical Wurtz and Grignard type couplings result in complex mixtures of symmetrical and unsymmetrical products with loss of double bond geometry and position in at least one of the units. Two more modern variants also suffer from lack of efficient cross-coupling.[1,2] Recently, three methods have been reported which avoid some of the problems associated with the allylic coupling route to 1,5-dienes.[3-5] We would like to report a new cross-coupling procedure that involves the reaction of an allylic halide with an allyllithium species generated in situ in a novel fashion, by reduction of the mesitoate ester of the corresponding allylic alcohol. Although partial allylic transposition in the nucleophile-derived portion of the resulting diene is still a problem, this method gives predominately cross-coupled products in fair to excellent yields and is operationally quite simple.

Treatment of equimolar amounts of an allylic mesitoate and an allylic bromide in tetrahydrofuran with excess lithium at 0° results in a mildly exothermic reaction. After a period of time ranging from twenty minutes to an hour, the reaction mixture turns a deep red-brown within a matter of seconds. Quenching with water immediately after the color change allows the isolation of the dienes A and B as the hydrocarbon fraction, mesitoic acid, and traces of several other materials of intermediate polarity. The yield and distribution of products are summarized in Table 1.

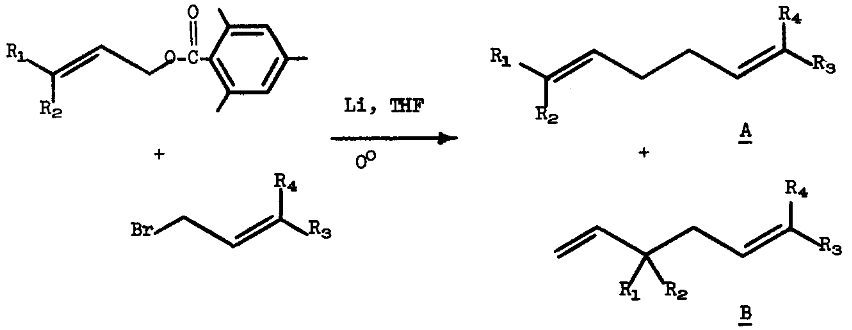


Table 1 Products and Yields from Cross-Coupling Reactions

	Mesitoate	Bromide	% Yield[a]	A : B	% Mesitoic Acid Recovered
1.	Geranyl	Geranyl	90	60:40	61
2.	Neryl	Neryl	90	60:19[b]	9
3.	Geranyl	Farnesyl	43	77:23	--
4.	Geranyl	Allyl	60 (35)	80:20	66
5.	Allyl	Geranyl	22	100: 0	37
6.	3-Methyl-2-butenyl	Geranyl	32	65:35	43
7.	Geranyl	3-Methyl-2-butenyl	(49)	72:18	73
8.	Crotyl	Geranyl	19	55:44	11

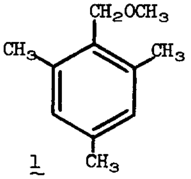
a) Measured by glpc using internal standards. Yields in parentheses are isolated.
b) Some products having *trans* (geranyl) geometry were also isolated.

From the results of the unsymmetrical couplings (3-8) it is quite clear that the nucleophilic fragment is derived from the mesitoate and not the bromide, as only the mesitoate-derived portion is subject to allylic transposition (product type B). Such transpositions are restricted to the organometallic portion in allyl organolithium coupling reactions.[6,7]

The efficiency of cross-coupling in this reaction is far better than that found in Wurtz or Grignard couplings as is evident from the much lower amounts of symmetrical products formed. Since coupling products are not formed when either geranyl mesitoate or geranyl bromide alone is treated under the same reaction conditions that result in the yield shown in Table 1 (reaction 1) it seems likely that the small amount of symmetrical products observed results from a metal-halogen exchange reaction.

There is a rather marked dependence of yield on the structure of both the mesitoate and the bromide. Yields are generally higher when both allyl systems are highly alkyl-substituted.

Mesitoic acid can be recovered in variable yields by sodium hydroxide extraction of the quenched reaction mixture. This indicates that the mesitoate portion is being consumed by a secondary process. Indeed, treatment of mesitoic acid alone with lithium in tetrahydrofuran resulted in the production of the deep red-brown color observed in the coupling reactions. A methyl iodide quench of this reaction mixture allowed the isolation of a number of reduction products, two of which were tentatively identified by spectroscopic properties as 1 and 2[11]; the structure of 1 was confirmed by an independent synthesis.



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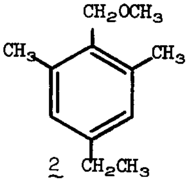

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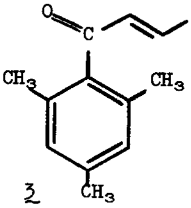

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We have attempted to use the reductive cleavage of allylic mesitoates to produce titratable amounts of organolithium reagents in a procedure analogous to Eisch's use of allyl phenyl ether.[9] However, at no point during the course of the consumption of allyl mesitoate does the amount of allyllithium become more than 12% of the theoretical yield (as measured by gas evolution). This indicates that in the absence of bromide, the lithium species is being consumed in a reaction with remaining ester. Reaction of allyl mesitoate with allyllithium prepared from allyl phenyl ether[9] does in fact give the α-β unsaturated ketone (3) in quite good yields. Treatment of allyl mesitoate alone with lithium or in the presence of geranyl bromide also gave significant amounts of 3, indicating that the reaction of the allyllithium with the ester carbonyl is an important side reaction in certain systems

We have attempted to extend the scope of this reaction to non-allylic systems; however, no coupling is observed when a primary alkyl group is substituted for allyl in either the mesitoate or the bromide. Furthermore, no coupling is detectable if an allylic benzoate is used in place of the corresponding mesitoate.

Work is currently in progress investigating the nature of non-hydrocarbon side products produced in this reaction and the utility of this type of reaction for the generation of carbinols when allylic bromides are replaced with ketones or aldehydes.

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7. There are several reports of couplings in which allylic mesitoates have reacted as electrophiles with alkyl and benzyl Grignard reagents.[8] These reactions were conducted in ethyl ether and in the absence of free metal, conditions under which our coupling fails to work. However, to establish unequivocably that the mesitoate is playing a nucleophilic role and that no 1,5-diene is produced from the reaction of allyl bromide-derived allyllithium with the mesitoate, the following experiment was conducted: Geranyllithium (formed from its phenyl ether)[9] was allowed to react with allyl mesitoate. No cross-coupling products could be detected, and the small amount of geranyl dimer observed was produced during the geranyllithium preparation[10] and was present prior to the attempted coupling.
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11. Spectroscopic evidence does not allow distinction between structure **2** and the isomer with the ethyl *ortho* to the methoxymethyl substituent.