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REACTIVITY OF THE 1-LITHIA-1-ZINCAALKENES. A FORMAL REGIOSPECIFIC ADDITION OF ALLYLZINC BROMIDE TO ALKENES. Part 4[1]

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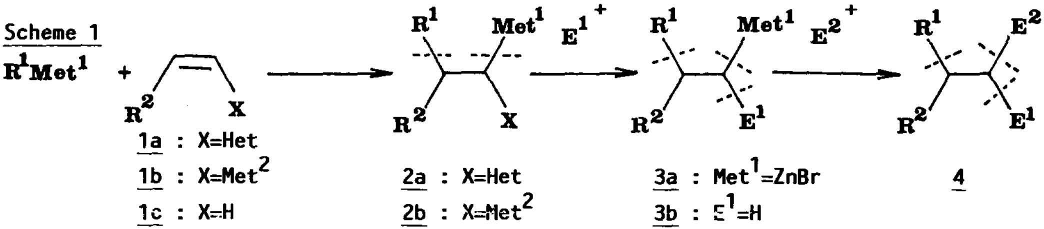
Summary : The 1-lithia-1-zincaalkenes, formed by the addition of allylzinc bromide to an alkenyllithium derivative, can be selectively mono-protonated, -deuterated, -stannylated or -alkylated leading to highly functionalized zinc compounds which by reaction with various electrophiles furnish polyfunctionalized products in good yields.

Scheme 1



The addition of an organometallic derivative (R^1Met) to a double bond of type 1a where X is a heteroatomic group (X=Het=SR, SOR, SO_2R, $PO(OR)_2$, NO_2) is a well known and very useful reaction. We reported recently[2] that such an addition reaction is also possible with a substrate of type 1b where X is a metal (X=Met^2=Li,MgBr or AlR_2) and an allylic zinc bromide leading to a gem-dimetallic compound of type 2b. This is a fairly general reaction which proceeds under mild conditions and with satisfactory to very good yields. The dimetallic reagent 2b which bears two different metals on one carbon atom should be able to react selectively, first with an electrophile E^1 leading to 3a, then with an electrophile E^2 leading to products of type 4. Preliminary results[2] show that such chemoselective reactions are indeed possible by using the alkenyl magnesium derivatives 1b (Met^2=MgBr). We report now that the alkenyl lithium compounds 1b (Met^2=Li) are far more versatile reagents for these gem-difunctionalizing reactions and allow the synthesis of various products of type 4 in good yields (see scheme 2). Three new carbon-carbon or carbon-heteroatom bonds are formed from 1b to 4, demonstrating that alkenyl lithium organometallics are powerful multi-coupling reagents[3]. If the first electrophile E^1 is a proton, then a formal addition of an allylic zinc derivative to an alkene (1c) has been realized (1c ⟶ 3b ; see scheme 1). Whereas the addition of organometallics to non-activated alkenes is a known reaction[4,5], its synthetic usefulness is sometimes hampered by the following difficulties :

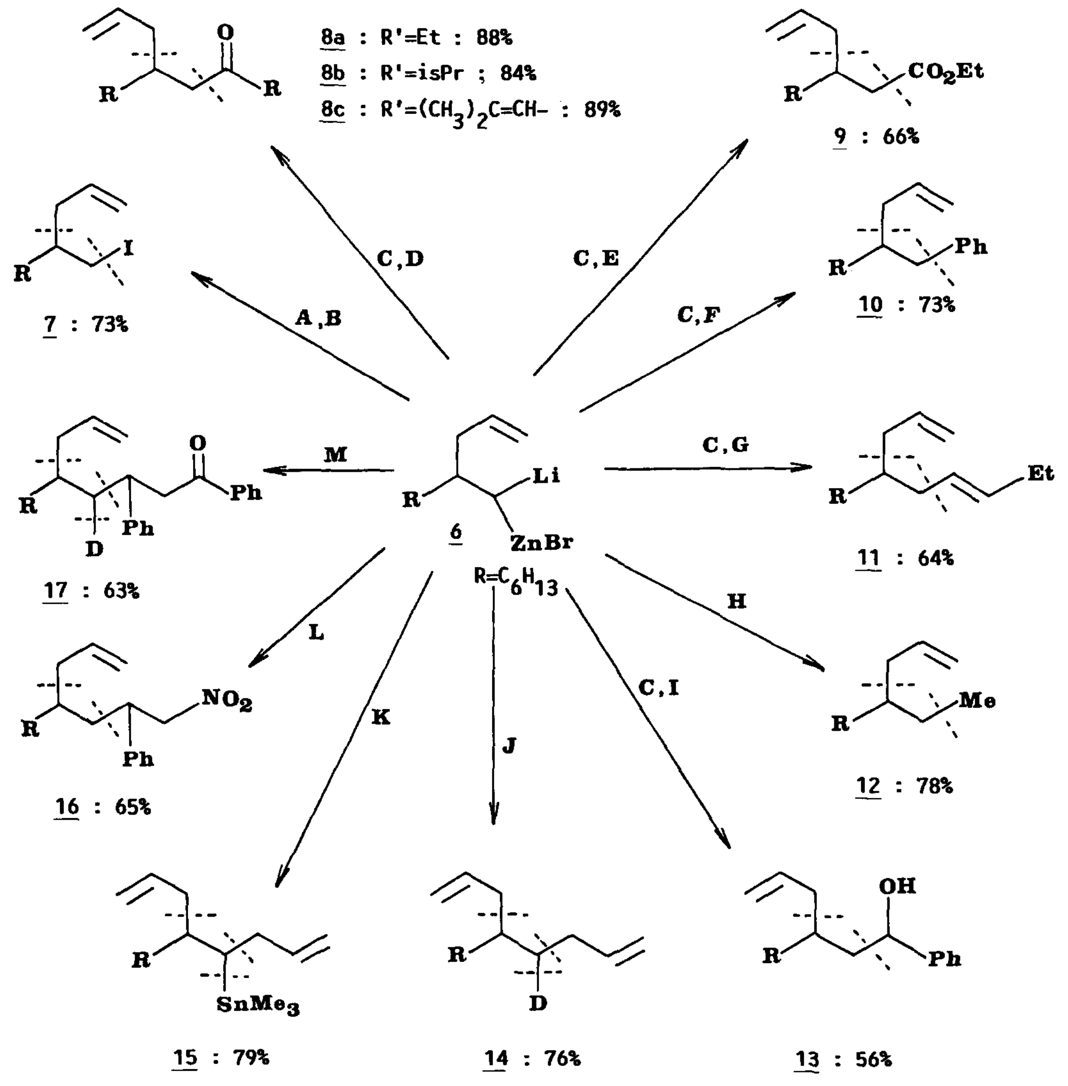
(i) an excess of the reagent $R^1Met^1_4$ or of the alkene 1c is necessary to achieve the insertion reaction leading to 3b[4] ;

(ii) the insertion step is not always regioselective[4];

(iii) the reaction of the formed organometallic 3b with an electrophile E^2 requires sometimes an excess of this electrophile[4] ;

(iv) the use of a stoichiometric amount of an expensive transition metal salt is sometimes necessary[5].

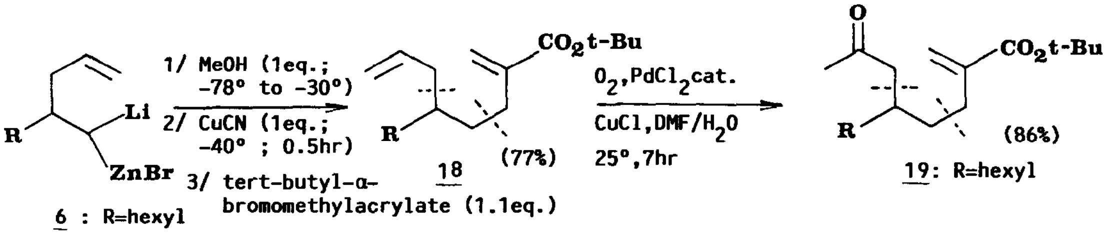
Scheme 2[15]



Reaction conditions : A:MeOH(1.05eq.; -70° to -30°); B:I_2(1eq.,-78° to -40°; 0.1hr); C:iso-BuOH(1.01eq.; -70°(slow add.) to -30°(0.3hr)); D:R^1COCl(2.5eq.); $Pd(PPh_3)_4$ (0.05eq.) 0°, 0.5-2hr); E:EtOCOCl(2.5eq.); $Pd(PPh_3)_4$(0.05eq.); 25°, 8hr; F:PhI(1.1eq.); $Pd(PPh_3)_4$ (0.05eq.); 25°, 4hr; G:(E)-iodo-1-butene(1.2eq.); $Pd(PPh_3)_4$(0.05eq.); 25°, 2hr;H:tert-BuSH (1.01eq.; -78° to -30°); then CuI(1.0eq.; -15°; 0.75hr); then excess MeI(5eq.; 25°; 4hr); I:$ClTi(OisPr)_3$(2eq.; -60°; 0.3hr); then PhCHO(1.5eq.: 25°: 22hr); J:MeOD(1.05eq.; -70° to -20°; 0.5hr); then CuCN(1eq; -40°; 0.25hr); then excess of allylbromide (-40° to 25°; 0.5hr) ;K:Me_3SnCl(1.0eq.; -40° to -30°; 1hr); then CuCN(1.0eq.; -30° ; 0.5hr); then allyl bromide(3.0eq.; -30° to -10°; 0.5hr); L :nitro-styrene (1.0eq.; -50°; 2hr); then H_3O^+ ; M : benzalacetophenone(1.0eq.; -78° to 0°; 1hr); then D_3O^+.

For all these reasons our method which uses stoichiometric amounts of reagents (1.1eq. of allylzinc bromide for 1.0eq. of the alkenyl lithium derivative) and shows complete regioselectivity[1,2] is an interesting alternative. As protonating agent, a THF solution of methanol(1.05eq.) is the most selective reagent[6]. Various electrophiles E^2 can be used and allow the synthesis of various classes of highly functionalized compounds (see scheme 2). The protonation of the in situ generated 1-lithia-1-zincaalkene 6 with methanol (1.05eq.), followed by treatment with iodine (1.1eq.) furnishes the iodoalkene[2] 7 (73%). The palladium catalyzed acylation[7] of the monoprotonated zinc compound obtained from 6 with acid chlorides and ethyl chloroformiate gives respectively the unsaturated ketones 8a-c and the ester 9 in high yields. A palladium (0) catalyzed coupling reaction[8] of the same zinc derivative with iodobenzene and (E)-iodobutene leads respectively to the benzene derivative 10 (73%) and to the (E)-diene 11 (64%) ; see scheme 2. A mono-alkylation with iodomethane can be performed by adding to the dimetallic reagent 6 successively tert-BuSH (1.01eq.), CuI (1.0eq.) to form a thioheterocuprate which reacts readily with an excess of iodomethane (4hr,25°) to furnish the alkene[2] 12 (78%). The reaction of an aldehyde with an alkylzinc bromide is a low yield reaction[9]. We have found that a transmetallation reaction of an alkylzinc bromide with $ClTi(OisPr)_3$[10,11] occurs readily and enhances thus considerably its reactivity towards aldehydes[12]. Using this result[12], we have treated the dimetallic compound 6 with sec-butanol (1.01eq.) then with $ClTi(OisPr)_3$(2eq.) and benzaldehyde (1,5eq.) which gives the unsaturated alcohol 13 in 56% yield (see scheme 2). The first electrophile E_1 may be different from a protonating agent and the 1-lithia-1-zincaalkene 6 reacts also selectively with methanol-d, Me_3SnCl[2] and some Michael-acceptors. For example if the electrophile E^1 is methanol-d (1.05eq.), after zinc-copper exchange[1] and treatment with an excess of allyl bromide, the deuterated diene 14 is obtained (76%). In the same way, the dimetallic compound 6 reacts successively with Me_3SnCl(1.0eq.), CuCN(1.0eq.) and an excess of allyl bromide to give the tin derivative 15 in 79% yield. Some powerful Michael-acceptors can also be used and the reaction of 6 with nitrostyrene leads to the nitroolefin 16 (65% yield) whereas the reaction of 6 with chalcone (1.0eq.) followed by quenching of the intermediate γ-zinca-enolate with D_2O followed by the usual work-up, leads to the specifically deuterated enone 17 in 63% yield (see scheme 2). To demonstrate the synthetic equivalence between an allylation reaction and an acetonylation reaction[13] we have treated the dimetallic reagent 6 successively with methanol (1eq.), CuCN(1eq.), tert-butyl-α-bromomethylacrylate (1.1eq.) and obtained the dienic ester 18 in 77% overall yield[15] (see scheme 3). Oxidation of 18 under the Wacker-Tsuji conditions[13](oxygen balloon, CuCl(1.0eq.), $PdCl_2$(0.05eq.) in DMF/H_2O (7:1), 25°, 7hr) furnishes the highly functionalized keto-ester 19 in 86% yield (see scheme 3).

Scheme 3[15]



Schemes 2 and 3 show that 1-lithio-1-zincaalkenes of type 6 allow the construction of various organic compounds, some of which are hard to synthetize by classical ways. The convergent aspect of our strategy (the alkenyllithium derivative 1b (Met^2=Li) is considered as a $a^2/d^1/d^1$ multi-coupling reagent[3,14] which is able to form successively three new bonds) and its high synthetic flexibility should have some utility in organic synthesis : the fine tuning of the reactivity of 6 by an appropriate transmetallation reaction allows the use of numerous types of electrophiles[1]. Further aspects of the reactivity of these and other gem-dimetallic compounds are currently studied.

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