Efficient Access to All-Carbon Quaternary and Tertiary alpha-Functionalized Homoallyl-type Aldehydes from Ketones

Efficient Access to All-Carbon Quaternary and Tertiary α-Functionalized Homoallyl Aldehydes from Ketones

Vittorio Pace,* Laura Castoldi, Eugenia Mazzeo, Marta Rui, Thierry Langer and Wolfgang Holzer

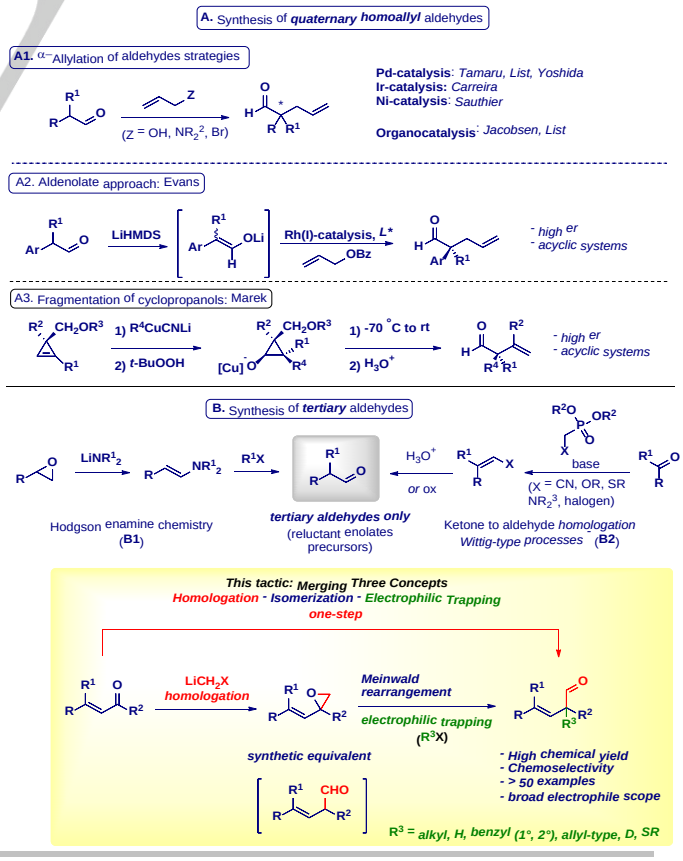
Abstract: Widely substituted all-carbon quaternary and tertiary α-aldehydes are rapidly assembled through a unique synthetic operation from ketones consisting in: 1) C_1-homologation; 2) epoxide-aldehyde Lewis acid mediated isomerization and, 3) electrophilic trapping. The synthetic equivalence between a vinyl oxirane and a β,γ-unsaturated aldehyde is the key concept for introducing such a previously undisclosed tactic. Mechanistic studies and labeled experiments suggest the intervention of an aldehyde enolate as the crucial intermediate. Significantly, the homologating carbenoid formation event (carbenoid precursor and organolithium) plays a critical role in determining the chemoselectivity.

The all-carbon α-quaternary aldehyde functionality constitutes an important motif across the chemical sciences.[1] From a reactivity perspective, the high electrophilicity of the aldehyde moiety represents an excellent tool for enabling chemistry juxtaposed to a bulky quaternary center. In this context, the *α-allylation* of aldehydes to obtain the corresponding homoallylic derivatives has been extensively investigated (Scheme 1 – A1). The introduction by Tamaru in 2001 of Pd-catalyzed chemistry (Tsuji-Trost) could be considered the breakthrough in the field.[2] Fine tuning of the reaction conditions put the bases for further highly enantioselective developments (List[3] and Yoshida[4]), which complemented previously known asymmetric organocatalytic (Jacobsen)[5] or stereodivergent dual catalytic (Carreira)[6] approaches. The process also benefited from switching to Ni-catalysis as disclosed – very recently - by Sauthier.[7] Interestingly in the case of simple linear aldehydes, the procedure enabled the development of a tandem aldol condensation/allylation protocol. The development of these strategies allowed also to overcome the reluctance of the conceptually simplest strategy based on the use of aldehyde enolates as nucleophiles in alkylation chemistry.[8] A major advancement in the field has been documented in 2016 by P. A. Evans who developed an enantioselective Rh-catalyzed allylation of prochiral α,α-disubstituted aldenolates with allyl benzoate (Scheme 1 – A2).[9] Furthermore, the selective ring fragmentation of diastereomerically pure and enantioenriched cyclopropanols represents a versatile tool for accessing acyclic *n*-butenals possessing the all-carbon quaternary stereocenters, as showed in elegant work by Marek (Scheme 1 – A3). In general, the high efficiency these methods showcase in terms of enantioselectivity or general applicability is counterbalanced by the limitation to access *homoallyl* or *allyl* α-quaternary aldehydes thus, leaving almost undisclosed the access to differently substituted all-carbon α-quaternary aldehydes. Prior to Evans' work,[9] the α-derivatization of aldehydes *via* enolate-type chemistry – albeit limited to the obtainment of α-tertiary species - has been achieved by Hodgson[10] *via* the epoxide-aldehyde isomerization (Scheme 1 – B1).[11] Accordingly, the treatment of a *mono*-substituted epoxide with a lithium amide hindered base provided a nucleophilic enamine susceptible of alkylation to finally afford α-substituted alkyl aldehydes. Remarkably, chiral lithium bases enabled high asymmetric induction.[12]

Analogously almost limited to the synthesis of *tertiary* α-aldehydes was the simple – but not fully explored[13] – homologation *i.e.* direct transformation of a ketone to an aldehyde (Scheme 1 – B2).[14]

Thus, the isomerization of an epoxide to an aldehyde under different conditions (*i.e.* Meinwald-type rearrangement triggered by a Lewis acid),[15] inspired us to employ the required epoxide as a naked *carbonyl equivalent* susceptible of α-functionalization with a given electrophile. In turn, the key-oxirane could be easily installed through the C_1-homologation of a ketone, as we recently reported.[16]

Herein, we present the versatility of the planned strategy to target α-quaternary aldehydes through a single synthetic operation consisting of: 1) *ketone homologation; 2) epoxide-aldehyde isomerization* and, 3) *α-derivatization*.



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Scheme 1. General context of the presented work.

At the outset of our investigations – in route to expand the 1,2-chemoselective addition of lithium carbenoids to α,β-unsaturated ketones[16a] - we considered the simply increase of temperature (-78 °C to rt)[17] enough for reaching the highly versatile vinyl epoxide[18] **2** directly from the enone **1**. To our surprise, we observed the formation of α-methyl aldehyde **3** as the unique reaction product in 89% isolated yield (Table 1 – entry 1). No trace of the expected epoxide **2** was evidenced in the ^{1}H-NMR of the reaction crude.[19]

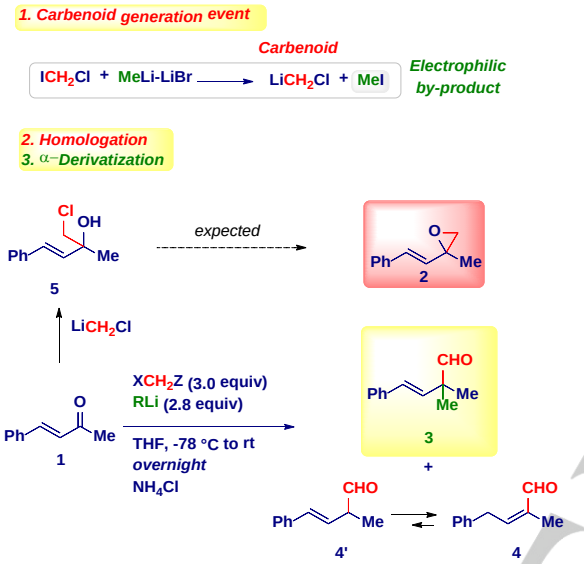


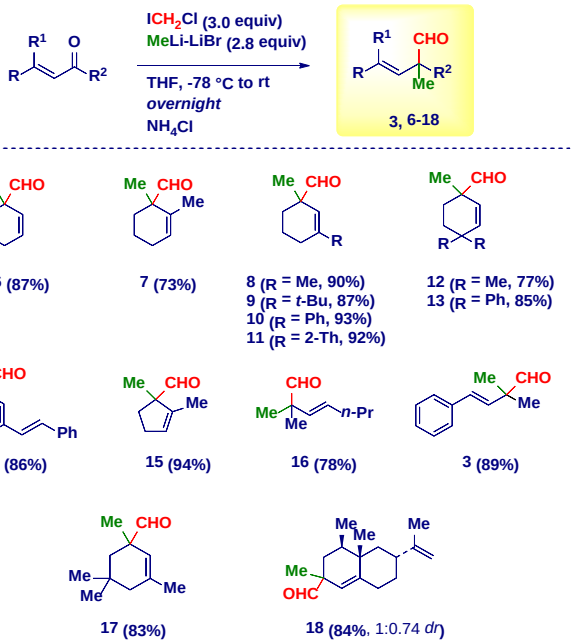
Table 1. Optimization of the reaction

Entry[a]	Carbenoid precursor	RLi	By-product generated	Ratio **3**:**4** Yield (%)
1	ICH_2Cl	MeLi-LiBr	MeI	1:0 (89%)
2	ICH_2Br	MeLi-LiBr	MeI	1:0 (83%)
3[a]	ICH_2Cl	*n*-BuLi	*n*-BuI	0:1 (66%)
4[a]	ICH_2Cl	$TMSCH_2Li$	$TMSCH_2I$	0:1 (90%)
5[a]	ICH_2Cl	PhLi	PhI	0:1 (80%)
6	$(n\text{-}Bu)_3SnCH_2Cl$	MeLi-LiBr	$(n\text{-}Bu)_3SnMe$[b]	0:1 (88%)
7[a]	ICH_2Cl	MeLi	MeI	1:0.7[c]

[a] LiBr 1.5 M in THF was added. [b] 82% isolated yield. [c] **3** 52% isolated yield, **4** 36% isolated yield. For additional optimization studies, see SI.

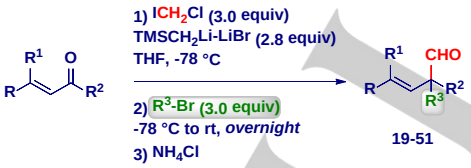
In order to fully understand this unusual transformation, the two separate occurring events (although under Barbier-type conditions)[20] were investigated (Table 1). The switching to a different 1,1-dihalomethane carbenoid precursor did not evidence any alteration in the products' ratio (entry 2). Two fundamental observations were deducted when the carbenoid was generated by employing different organolithium reagents (RLi) or carbenoid precursors (XCH_2Z). Accordingly, by forming the carbenoid with *n*-BuLi, PhLi or $TMSCH_2Li$, the reaction afforded exclusively the β,γ-unsaturated *non*-substituted aldehyde **4'** (which isomerized spontaneously to the more stable α,β-unsaturated one **4**).[21] Such a behavior suggested the electrophilic by-products – less reactive than MeI - obtained during the carbenoid formation event (*n*-BuI, PhI, $TMSCH_2I$, respectively) might be involved in the process (entries 3-5). Furthermore, generating the carbenoid *via* Li/Sn transmetallation[22] (entry 6) provided, once more, as the unique product again **4** and, interestingly, the corresponding stannane by-product [$(n\text{-}Bu)_3SnMe$] could be isolated after chromatographic purification. Combining these results, it seemed likely the source of methyl unit could arise from the methyl iodide (MeI) delivered during the generation of the carbenoid ($LiCH_2X$, X = Cl, Br) in the presence of MeLi-LiBr. One additional point merits mention: the presence of the Lewis acid (*e.g.* LiBr)[23] and the increase of temperature from -78 °C to rt were essential for enabling the α-quaternarization. Performing the reaction with LiBr-free MeLi gave a 1:0.7 mixture of **3**:**4** (entry 7), while keeping the reaction – even for prolonged time (24 h) - at -78 °C afforded the simple halohydrin **5** in 91% yield.

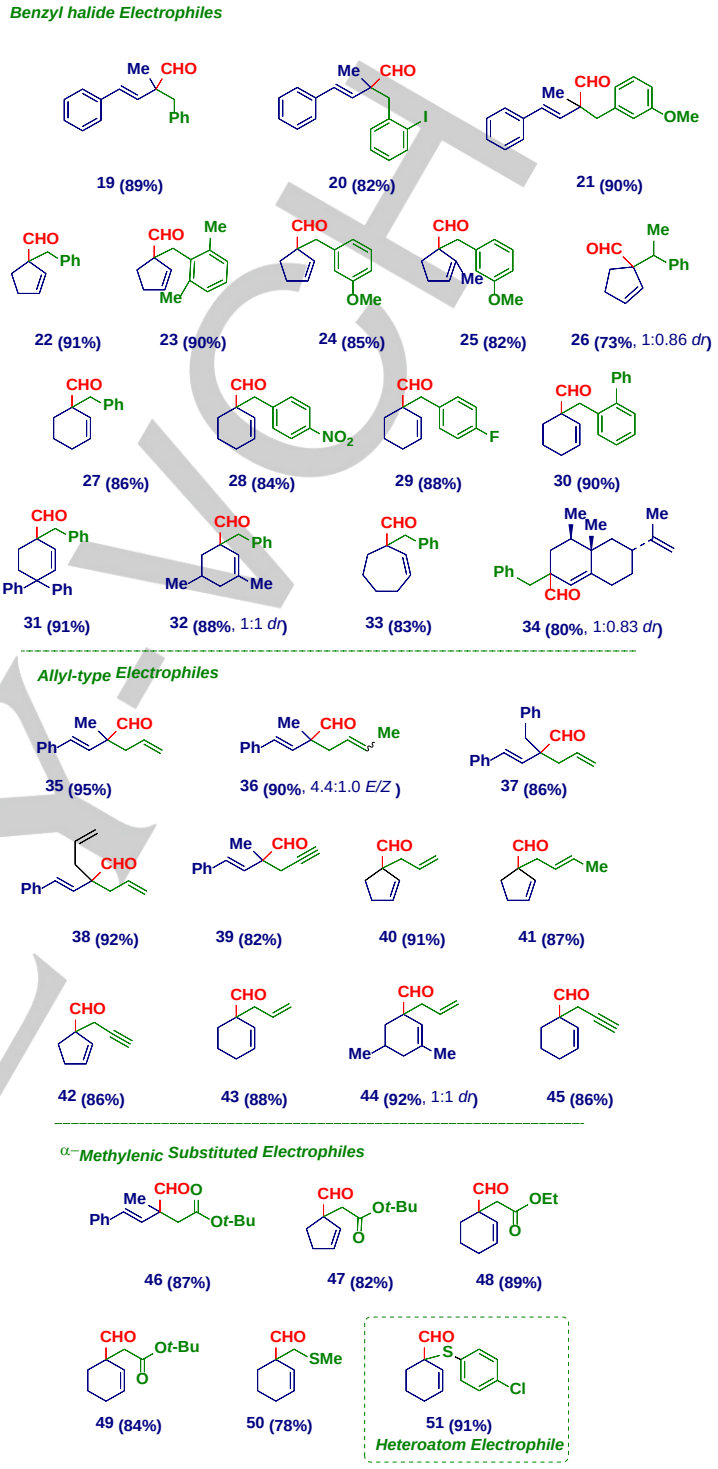
As outlined in Scheme 2, quaternary α-methyl aldehydes (Scheme 2) were rapidly prepared under the optimized conditions. The reactions proceeded cleanly, in high chemical yields regardless the nature [cyclic (**6**-**15**) or acyclic (**3**, **16**)] of the substrates and the substitution pattern across the starting ketones. We anticipate our method allowed to access important α-methyl aldehydes (*e.g.* **8-10**) – used as materials for a plethora of chemical transformations[24] – in just *one* chemical operation, without needing to employ multi-steps (four) and complex procedures routinely employed.[25] Gratifingly, also more complex natural products (isophorone and nootkatone) underwent this novel high-yielding transformation (**17**-**18**).



Scheme 2. Direct synthesis of quaternary α-methyl aldehydes.

The feasibility of the protocol for the efficient building up of quaternary α-methyl aldehydes, allowed us to endeavour the more challenging fully substituted ones, featuring a residue proceeding from a second – *added* - electrophile. Based on the optimization study (Table 1, entry 4), we considered $TMSCH_2Li$-LiBr the ideal reagent to generate the $LiCH_2Cl$ carbenoid. As shown before, $TMSCH_2I$ arising from the carbenoid formation event is completely unreactive towards the intermediate epoxide. Pleasingly, by simply adding 3 equiv of an electrophile, the tactic could be successfully extended for the high yielding, chemoselective obtainment of all-carbon quaternary α-functionalized aldehydes (Scheme 3). Benzyl halides proved to be excellent partners for the reaction without significant difference in reactivity played by the starting carbonyl species (**19**-**34**). The following points merit mention: 1) the presence of a potentially exchangeable iodine did not alter the chemoselectivity (**20**); 2) the substitution across the aromatic ring of the benzyl halide is well tolerated (**23**-**25**, **28**-**30** - noteworthy the presence of a nitro group); 3) no decrease in reactivity was observed when sterically hindered benzyl halides were used (**23**) or when the starting carbonyl featured a substitution at the α-position (**25**); 4) a secondary benzyl bromide could be used for trapping, albeit in lower yield (**26**); 5) the bicyclic natural product nootkatone was amenable also for the α-benzylation (**34**). Unsaturated functionalities containing halides (allyl, crotyl, propargyl) served as well as excellent trapping agents for the transformation for both acyclic (**35**-**39**) and cyclic systems (again without effect of the ring size, **40**-**45**). Analogously, multielectrophilic partners such as α-bromo esters did react according to the general scheme, providing interesting γ-oxo esters (**46**-**49**). The trapping with an α-halomethyl sulfide provided the β-sulfur substituted aldehyde **50** in comparable chemical yield. The tactic was amenable for extending the applicability to a quaternary α-heteroatom aldehyde as showcased by the example with a sulfur electrophile [$(4\text{-}ClC_6H_4S)_2$, **51**].

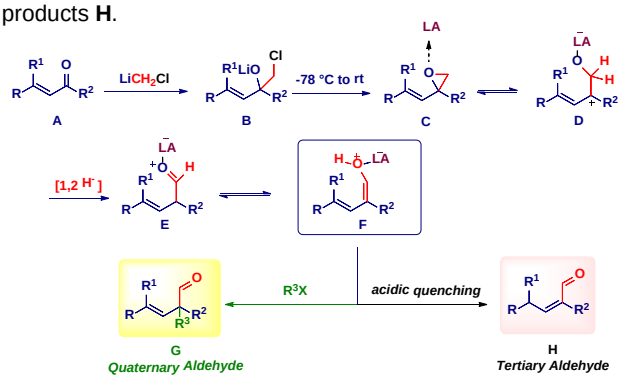




Scheme 3. Synthesis of fully substituted quaternary α-methyl aldehydes.

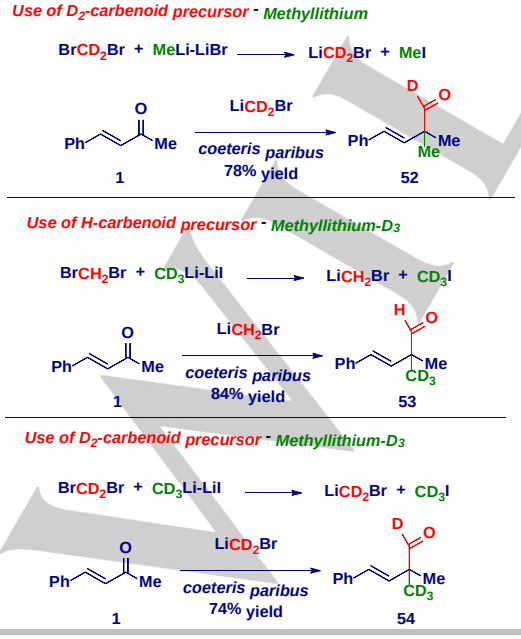
The mechanism of the transformation could be rationalized as follows (Scheme 4). The attack of the nucleophilic $LiCH_2Cl$ to the carbonyl compound **A** produced the *O*-lithiated halohydrin **B**,

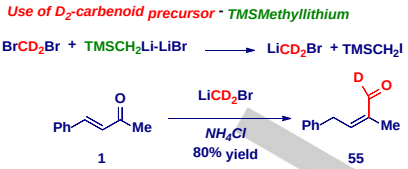
which upon increase of temperature cyclized to the vinyl epoxide **C**. In agreement with Lautens' work on the amphoteric character of vinyl oxiranes,[26] the Lewis acid (LiBr) triggered the ring opening – favored by the formation of the allylic carbocation **D** – to furnish - *via* 1,2-hydride shift and tautomeric equilibrium - the enolate **F**. The latter could then react with an adequate electrophile yielding the quaternary aldehydes **G** or, alternatively upon simple acidic quenching and tautomerization the tertiary products **H**.



Scheme 4. Plausible mechanism.

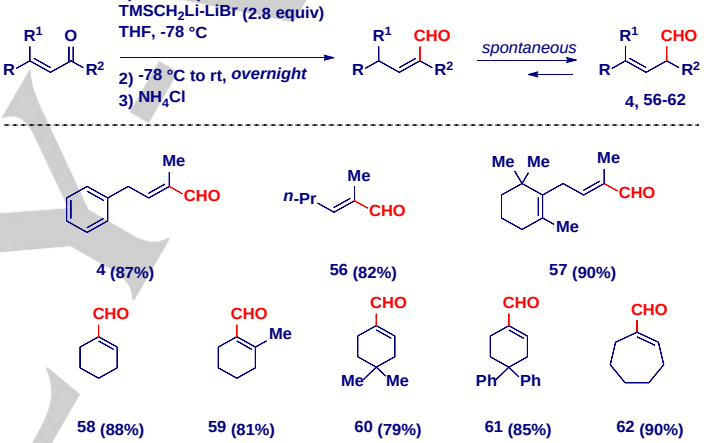
In order to gain definitive proof on the enolate-type mechanism, additional experiments with deuterium labeled carbenoids and/or methyllithium were conceived (Scheme 5). 1) The use of the deuterated carbenoid $LiCD_2Br$ generated from CD_2Br_2 and MeLi-LiBr afforded the aldehyde **52** presenting a α-C*H*$_3$ group and a deuterated carbonyl. 2) The employment of $CD_3Li{\cdot}LiI$ and CH_2Br_2 – which evidently forms $LiCH_2Br$ – gave the *H*-aldehyde **53** featuring the C*D*$_3$ group at the α-position. 3) The homologation with $LiCD_2Br$ – formed from CD_2Br_2 and $CD_3Li{\cdot}LiI$ – yielded the aldehyde **54** showing deuteration at both sites: the aldehyde and the α-position. 4) Homologating with $LiCD_2Br$ generated with $TMSCH_2Li$ and quenching with an acid, delivered the deuterated α,β-unsaturated aldehyde **55**. Thus, the whole reactivity is determined by the general equation for forming the nucleophilic carbenoid.





Scheme 5. Mechanistic proof for elucidating the formation of the enolate intermediate with deuterated species.

In agreement with the postulated mechanism (Schemes 4-5), with the aim of taking full advantage of the potentiality of the methodology, we smoothly accessed α-tertiary aldehydes – *i.e.* β-γ unsaturated - through the one-step homologation – isomerization procedure (Scheme 6). Significantly, during the work-up and purification procedure, the β-γ unsaturated aldehydes spontaneously isomerized to the more stable α,β-unsaturated ones (**4**, **56**-**62**). The substrate scope was broad and, interestingly, an important intermediate (**57**) for the synthesis of vitamin D[27] were targeted in a single high-yielding synthetic operation.



Scheme 6. Synthesis of α,β-unsaturated aldehydes through homologation-isomerization followed by acidic quenching.

In conclusion, we documented a rapid and high-yielding synthesis of all-carbon α-quaternary aldehydes starting from α,β-unsaturated (acyclic and cyclic) ketones. The single-step transformation stems on the merging of three concepts, namely homologation, epoxide-aldehyde isomerization and functionalization with an added electrophile (carbon or heteroatom) of the putative aldehyde enolate, whose intervention was proved through labeled experiments. For the first time, the effect of the lithium organometallic species employed for generating a carbenoid and the nature of the carbenoid precursor were found to be critical for the chemoselectivity. The protocol showcases an excellent substrate scope, enabling also the access to α,β-unsaturated aldehydes whenever no external electrophile was added. Currently, we are investigating the development of an asymmetric version of the protocol.

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Keywords: Homologation • Enolate • Carbenoid • Isomerization • Trapping

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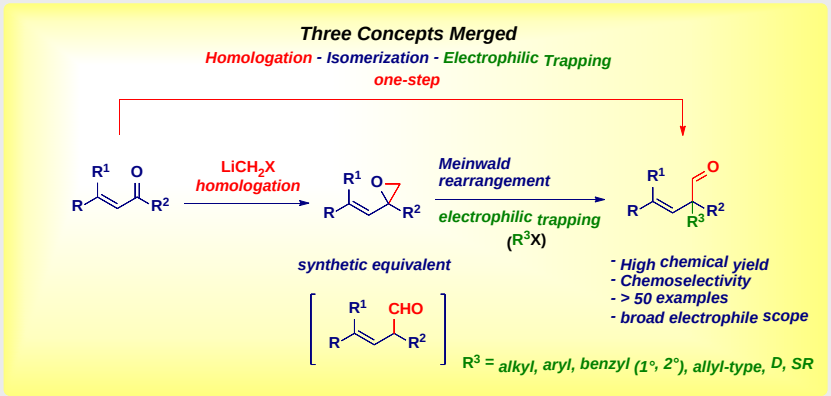

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