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Direct and straightforward transfer of C1 functionalized synthons to phosphorous electrophiles for accessing *gem*-P-containing methanes†

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The direct transfer of different α-substituted methyllithium reagents to chlorinated phosphorous electrophiles of diverse oxidation state (phosphates, phosphine oxides and phosphines) is proposed as an effective strategy to synthesize geminal P-containing methanes. The methodology relies on the efficient nucleophilic substitution conducted on the P-chlorine linkage. Uniformly high yields are observed regardless the specific nature of the carbanion employed: once established the conditions for generating the competent nucleophile (LiCH$_2$Hal, LiCHHal$_2$, LiCH$_2$CN, LiCH$_2$SeR *etc.*) the homologated compounds are obtained *via* a single operation. Some P-containing formal carbanions have been evaluated in transferring processes, including the carbonyl-difluoromethylation of the opioid agent Hydrocodone.

Organophosphorus compounds represent a highly versatile class of reagents, whose general reactivity is imparted by the unique features of the P–C bond.[1] The constitutive vicinal dipole (*i.e.* the so-called ylide motif)[2] – generated upon the proper modulation of the reaction conditions – is the pivotal factor enabling the reach chemistry achievable with these reagents. In this context, the venerable Wittig (and related) olefination processes document the high significance and the impact that organophosphorus chemistry continue to play in modern synthesis.[3] Moreover, the stereoelectronic characteristics of the P–C linkage are highly appreciated in drug design because of the mimicking effect towards critical phosphorous-based enzymes.[4] It is evident that the further derivatization on the carbon atom attached to phosphorus enables to diversify the resulting adduct and, ultimately, to widen the synthetic portfolio of transformations achievable with these reagents.[5] In fact, the introduction of a substituent such as an halogen profoundly influences the chemical behaviour of the species [R$_2$P(O)-CH$_2$-X] which formally becomes a C1-synthon amenable for homologation chemistry.[5,6] Structurally, the reagent manifests the fundamental feature of classical homologating reagents exemplified by the so-called metal carbenoids (*i.e.* MCH$_2$X).[7] Unfortunately, the disruptive α-elimination[8] – provoked by the internal coordination between a highly electropositive metal (*e.g.* Li) and the X group (usually a halogen) – makes the productivity of the reagent highly dependent on the conditions adopted for a given transformation (Scheme 1 – path a).[7a,9] It is worth noting that taming the electropositive character of the metal of the carbenoid emerged as an effective solution to increase the chemical integrity of MCH$_2$X species.[10]

In this context, our group recently documented this concept in the case of α-halomethyl- tin and germanium species that can be conceived as chemically stable sources for CH$_2$X and related CHXY fragments.[11] This logic is levered on the shuttle-type transfer of a reactive halomethyl (but not limited to) unit from the sensitive lithium cation (inherently sensitive) to the chemically stable 14th group elements. Mechanistically, the process involves an intuitive nucleophilic substitution on the metal (Sn and Ge) conducted with LiCHXY reagents.

We reasoned that an analogous rationale can be applied to R$_2$P(O)-Cl systems for the selective synthesis of R$_2$P(O)CH$_2$X reagents whose previous preparations were particularly challenging and, in many instances, requiring at least two chemical operations (Scheme 1 – path b). A survey of the available methods for accessing the title compounds indicates that the characteristic CH$_2$-X group is *per se* present or directly achievable from a thereof immediate precursor. For example, the expensive (chloromethyl)phosphonic dichloride has been used for this purpose and surmised to a sequential double nucleophilic substitution with an alcohol.[12] It appears evident that the requirement for the pre-installation of the CH$_2$X fragment makes the method not suitable for the modular synthesis of differently substituted analogues (*i.e.* change of the diversify-

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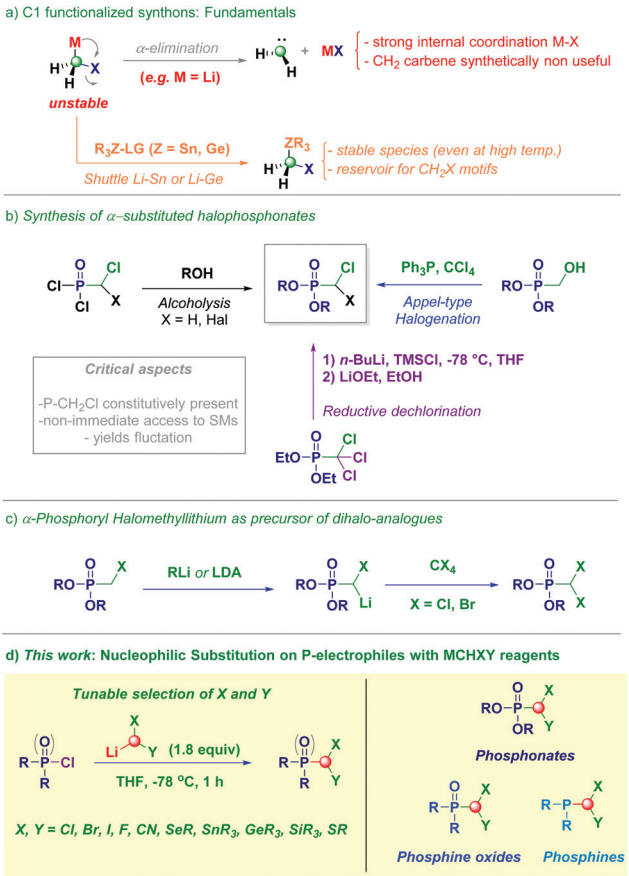


Scheme 1 General context of the presented work.

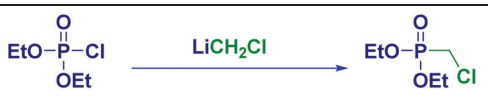
ing element X). Moreover, the Appel-type chlorination of diethyl(hydroxymethyl) phosphonate has been considered an alternative, although the fact that non uniform yields were obtained poses issues for the large scale application.[13] The reductive dechlorination of trichlorophosphonates in the presence of an alkyllithium afforded the title motifs, as well:[14] however, the difficulties in accessing the starting materials severely limits the adoption of the strategy in common synthetic processes. It is interesting to note that also the synthesis of α,α-dihalomethyl analogues is plagued by similar shortcomings and follows an analogous rationale. Additionally, because of the positive modulating effect exerted by a phosphonate on a putative α-halomethyl carbanion, the halogenation under electrophilic regime may also constitute an access to dihalomethyl derivatives (Scheme 1 – path c).[15]

Cognizant of the conceptual simplicity of transferring an α-functionalized methyl-type carbanion onto an electrophilic platform, as recently documented by our group,[16] herein we report a straightforward approach enabling the selective and precise delivery of nucleophilic elements (*e.g.* LiCHXY – X, Y = Cl, Br, I, F, CN, $SnBu_3$, $SiMe_3$) to different electrophilic [P(v), P(III)] phosphorous-centred manifolds (Scheme 1 – path d).[17] We anticipate the strategy is fully flexible and adaptable to prepare through a single synthetic operation the targeted structure starting from wide available and cost effective P-chloride materials. This is, upon generating the carbanion-type unit, the geminal phosphorous-containing α-substituted methanes are obtained in high yield and purity.

Diethyl chlorophosphate **1** was selected as the model substrate for evaluating the interrupted homologation with the carbenoid $LiCH_2Cl$ formed *via* I/Li exchange from ICH_2Cl and MeLi-LiBr at −78 °C under Barbier-type conditions. (Table 1). The use of a stoichiometric loading of nucleophile permitted to prepare the chloromethyl derivative **2**[18] – as the unique reaction product – in a moderate isolated yield of 41%, despite the GC-MS analysis showed 63% conversion (entry 1). Presumably, the significant loss of material during the chromatographic purification was due to decomposition activated by the silica gel. Unfortunately, the switching to a different stationary phase such as Florisil or neutral Alox (Brockmann II)[19] did not afford the isolated compound in comparable yield to the measured conversion (entries 2–3). We speculated that pushing the reaction towards completion by reacting **1** with supra-stoichiometric quantities of nucleophile could minimize the product's loss during the purification. Thus, the progressive increase of the carbenoid quantity resulted in a positive effect on the ratio conversion/isolated yield, being 1.8 equiv. the optimal one (entries 4–6). Some additional aspect merit mention: (a) the employment of a more stable (and less reactive) magnesium carbenoid was ineffective in promoting the reaction (entry 7);[20] (b) genuine selectivity for the substitution at the level of the P–Cl bond was manifested, leaving unaffected the two P-OEt ones.

With the optimized condition in hand, we then commenced the study of the scope of the homologative functionalization with differently α-substituted methyllithiums (Scheme 2). Not only $LiCH_2Cl$ acted as a competent nucleophile for the reaction (**2**) but, also $LiCH_2I$[21] and the highly

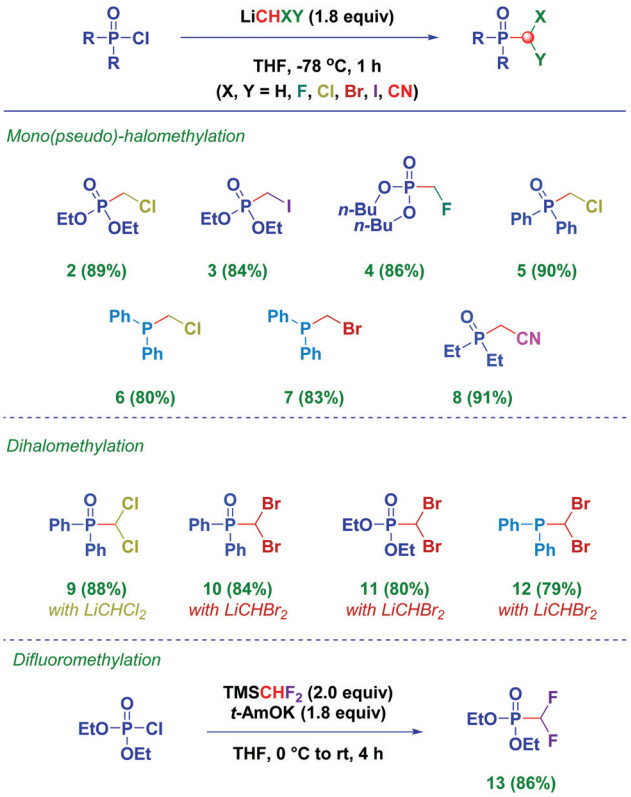
Table 1 Reaction optimization[a]



1 **2**

Entry	Carbenoid (equiv.)	Stationary phase	Conversion[b] (%)	Yield of **2**[c] (%)
1	$LiCH_2Cl$ (1.0)	SiO_2	63	41
2	$LiCH_2Cl$ (1.0)	Florisil	65	40
3	$LiCH_2Cl$ (1.0)	AloxN-BG2	63	38
4	$LiCH_2Cl$ (1.5)	SiO_2	82	71
5	$LiCH_2Cl$ (1.8)	SiO_2	94	89
6	$LiCH_2Cl$ (2.3)	SiO_2	96	90
7[d]	$ClMgCH_2Cl$-LiCl (1.8)	—	—	—

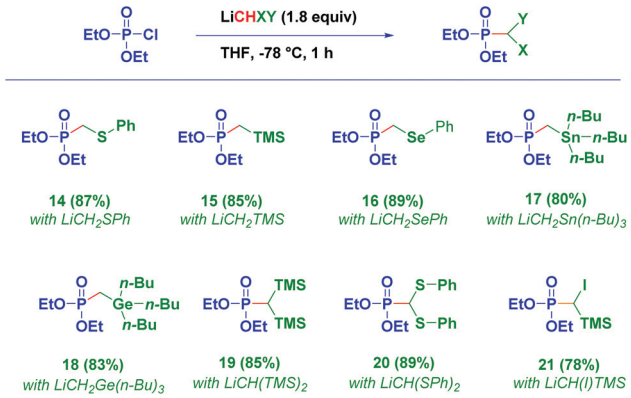
[a] $LiCH_2Cl$ was generated from ICH_2Cl and MeLi-LiBr in THF at −78 °C (see the ESI† for full details). [b] GC-MS calculated conversion: % GC conv. = [peak area (chlorophosphate 1)/{peak area (chlorophosphate 1) + peak area (chloromethyl phosphate 2)}] × 100. [c] Yields refer to isolated and purified compounds. [d] Formed from ICH_2Cl and i-PrMgCl-LiCl in THF at −78 °C under *non* Barbier conditions.



Scheme 2 Chemoselective homologative α- and α,α-difunctionalization of P(v) and P(iii) chlorides with carbenoid and carbanion-like nucleophiles.

unstable $LiCH_2F$[22] could be used for accessing phosphonates such as the iodo-analogue (**3**) and the fluorinated, highly versatile,[23] derivative (**4**). The methodology afforded, as well, the chloromethyl-derivative (**5**) of a phosphinic chloride, thus indicating the irrelevance of the oxidation state of phosphorous for enabling the transformation. This was further showcased in the interrupted homologation of chlorophosphine (trivalent P) which smoothly underwent the process with $LiCH_2Cl$ (**6**), $LiCH_2Br$[24] (**7**) and the non-carbenoid $LiCH_2CN$[25] (**8**). The trivial change of the metalation conditions of dihalomethanes (from halogen/Li to proton/Li permutation) generated the corresponding dihalocarbenoids[26] for carrying out the corresponding nucleophilic displacements. In analogy to the monohalomethyl units above presented, no difference in the reactivity of phosphinic- (**9–10**), phosphate- (**11**) and rare phosphine- (**12**) chlorides was noticed. Because of the inherent high instability of the difluoromethyl carbanion, the alkoxide-mediated activation of the commercially available $TMSCHF_2$, recently reported by us,[27] was effective for extending the methodology to introduce the versatile CHF_2 group (**13**).

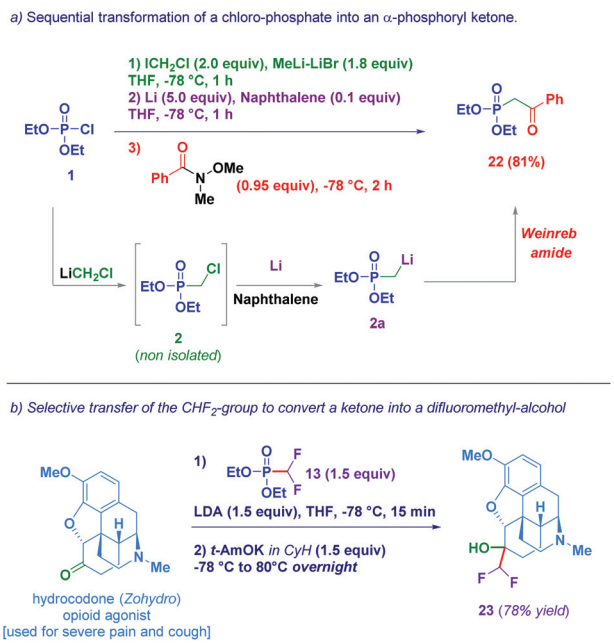
The strategy was of general applicability and enabled the P-functionalization with a series of various lithiated α-substituted methyl carbanions [α-thio- (**14**),[28] α-silyl- (15), α-seleno- (**16**),[29] α-stannyl- (**17**), α-germanyl- (**18**) – Scheme 3]. Moreover, the deprotonation of disubstituted methanes with a



Scheme 3 Nucleophilic substitution on chlorophosphates with variously functionalized α-substituted organolithiums.

lithium amide base furnished geminal tertiary carbanions [$(TMS)_2CH$- (**19**), $(PhS)_2CH$- (**20**), (TMS)ICH- (**21**)] which were smoothly transferred to the P-electrophiles, giving the corresponding functionalized phosphonates in high yield and selectivity.

With the aim of gaining full insight into the synthetic potential of the prepared α-methyl-substituted phosphorous species, selective transformations for the rapid introduction of these C1 building blocks into organic arrays were designed (Scheme 4). Firstly, we conceived an halomethylation – lithiation – electrophilic trapping sequence for converting directly a chlorophosphate into an α-phosphoryl ketone (path a). Indeed, the chloromethyl derivative **2** – formed under the established conditions and non-isolated – was subjected to reductive naphthalene-catalyzed lithiation with Li metal.[30]



Scheme 4 Synthetic usefulness of α-halosubstituted *gem*-P.

Subsequently, the so prepared α-phosphoryl-methyllithium carbanion **2a** very efficiently acylated with a Weinreb amide,[31] furnishing the ketone **22** in 81% isolated yield. Secondly, because of the well-known instability of carbanionic CHF_2 fragments,[27] we wondered if the stable difluoromethyl phosphonate **13** could act as a suitable transfer agent (path b). To this end, we selected the opioid agonist Hydrocodone (dihydrocodeinone) as a competent carbonyl-containing manifold for the introduction of the CHF_2 group. Pleasingly, the consecutive lithiation–nucleophilic addition–dephosphorylation strategy afforded the difluoromethyl alcohol **23** in high yield. The transformation presents some aspects worth of note: (a) the CHF_2-containing phosphonate represents an attractive synthon for the delivery of the difluoromethyl unit under nucleophilic regime, thus complementing the usually employed silicon-analogues;[27] (b) the facile access to compound **23** – conjugating the OH group (responsible for high opioid activity) and the drug-design interesting motif CHF_2 – may spur further studies in the area of novel morphinane-skeleton narcotic agents.

In summary, we disclosed a one-step functionalization of different chloro-phosphorous electrophiles (phosphates, phosphine oxides and phosphines) with α-substituted organolithium reagents (LiCHXY) for the direct obtainment of geminal P-containing methanes. Not only nucleophilic (di)-halocarbenoid ($LiCH_2Cl$, $LiCH_2I$, $LiCH_2F$, $LiCHCl_2$, $LiCHBr_2$) could be employed but, also a plethora of functionalized methyllithiums, such as $LiCH_2$-FG (FG = CN, SR, SeR, SiR_3, SnR_3, GeR_3) and LiCHXY (X, Y = I, SiR_3, SR) promoted the transformation. This modular, high yielding strategy relies on a conceptually intuitive straightforward nucleophilic substitution conducted with the nucleophilic element on the P–Cl linkage. The fine tuning of the conditions requested for generating the carbanion-like reagents is the unique factor to be taken into account for designing the process. The synthetic application of the accessed motifs has been screened in selective transformations, including the difluoromethylation of the carbonyl moiety of the narcotic agent Hydrocodone.

Conflicts of interest

There are no conflicts to declare.

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