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Modular and Chemoselective Strategy for Accessing (Distinct) α,α-Dihaloketones from Weinreb Amides and Dihalomethyllithiums

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Abstract. The selective transfer of diversely functionalized dihalomethyllithiums (LiCHBrCl, LiCHClI, LiCHBrI, $LiCHCl_2$, $LiCHBr_2$, LiCHFI) to Weinreb amides for preparing *gem*-dihaloketones in one synthetic operation is reported. The capability of these amides as acylating agents and, the wide availability of dihalomethanes as pronucleophiles, enable a straightforward route to the title compounds under full chemocontrol. No racemization phenomena were evidenced in the case of optically active materials. Additionally, tolerance to sensitive functional groups (esters, amides, halogens, olefins *etc.*) was uniformly noticed, thus making this conceptually intuitive strategy flexible and tunable by the operator.

Keywords: Ketones; Carbenoids; Halogen; Nucleophilic substitution; amides.

Introduction

The contemporaneous presence of a ketone functionality and two halogens at its vicinal position profoundly influences the physical-chemical and reactivity profile of the resulting array.[1] Evidently, introducing the two halogens serves as an intuitive strategy for tuning the pharmacokinetic profile (*e.g.* lipophilicity, protein interaction), thus making them structures of primary importance in drug design.[2] As a consequence, the significant relevance displayed by the so obtained α,α-dihaloketones in chemistry can be ascribed to two main factors: a) the increased carbon electrophilicity and, b) the enhanced acidity of the methinic proton (Scheme 1). Collectively, these synthons not only manifest high versatility in synthetic chemistry as precursors of valuable heterocycles or direct derivatives[3] [*e.g.* dihalohydrins (chloramphenicol)] but also, as more recently has been documented, they possess intrinsic biologically activity spanning from antibacterial to anticancer[4] or anti-HIV properties.[5] By mimicking the halogenase-mediated biosynthetic pathway,[6] methylketones (or thereof precursors such as alkynes)[7] emerged as prototypal starting materials for preparing α,α-dihaloketones in electrophilic regime.

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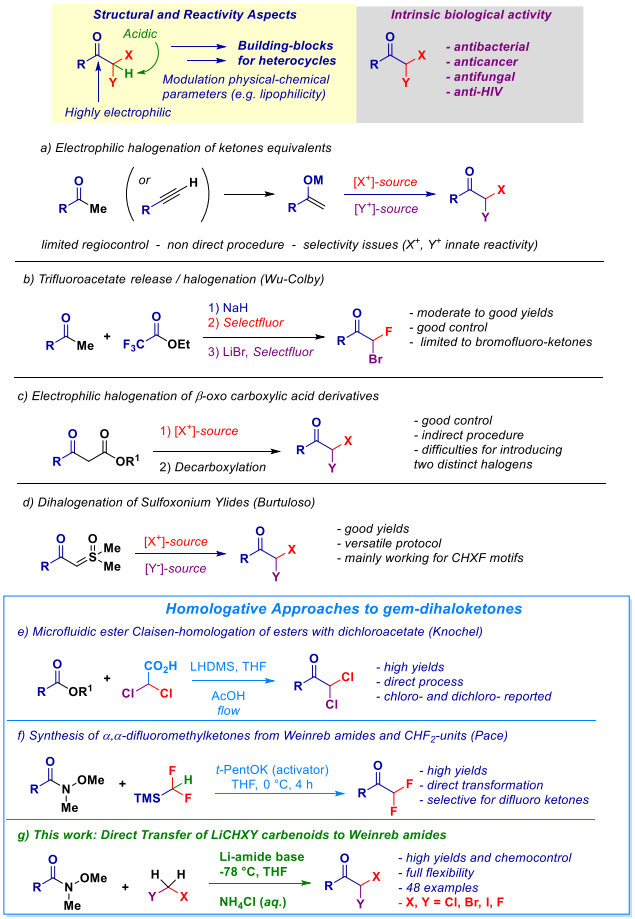

Scheme 1. State-of-the-art of *gem*-dihaloketones: properties and main synthetic procedures.

Mechanistically, upon the formation of a proper halonium species, two consecutive introductions of the halogens into the enol-type intermediates (enol ethers, enamines) take place giving the dihalo-geminal ketones (Scheme 1 – *path a*).[8] Unfortunately, the regiocontrol of the process remains elusive and, further complicated when the operation involves the insertion of two distinct halogens.[9] In this context, the Wu's modification[10] of Colby's protocol[11] paved on an initial nucleophilic substitution of an enolate on a trifluoromethyl ester of methylketones followed by halogenation constitutes a significant advancement allowing the preparation of variously functionalized fluoro-haloketones (Scheme 1 – *path b*). Moreover, discrete improvement of regiocontrol has been achieved through the formal geminal dihalogenation of β-oxo carboxylic derivatives (esters or acids).[12] Although effective and, in particular instances occurring with enantioinduction,[13] the requirement for the extra decarboxylation step renders the procedure not direct (Scheme 1 – *path c*). With the aim to improve the control of the halonium attack, putative α-oxo-carbanions resulted as interesting and valuable solutions.[14] Indeed, *gem*-dihalogenation procedures firstly conducted on α-diazo carbonyls, could be efficiently adapted to safer sulfoxonium ylides, as very recently documented in the elegant work of Burtuloso.[15] The methodology enables a straightforward, single step access to geminal difunctionalized ketones (α-alkyl-α-halo and α,α-dihalo) working under an innovative dual electrophilic-nucleophilic mode (Scheme 1 – *path d*). Notably, while the first halogen is introduced under electrophilic conditions, the second one is delivered from a halide donor species (NaX, TBACl).

The logic of introducing through an interrupted homologation process[16] a nucleophilic synthon CHXY into a recipient acylating agent can be regarded as a conceptually distinct alternative circumventing *de facto* the limitations raised above. Indeed, such an approach would precisely afford the targeted dihaloketone featuring the *exact* degree of halogenation requested in a direct fashion through a single synthetic operation.[17] Knochel demonstrated the validity of this assumption by adopting a microfluidic ester Claisen-type homologation approach to α-chloro and α,α-dichloroketones, being mono- or di-chloroacetate the nucleophilic *reservoir* (Scheme 1 – *path e*).[18] In 2019, our group developed an effective tactic for assembling tertiary difluoromethyl ketones *via* the direct attack of a nucleophilic difluoromethylated synthon to a Weinreb amide as the competent acylating agent.[19] Cognizant of the extreme liability of fluorinated carbanions, we found highly beneficial using $TMSCHF_2$ as the pro-nucleophile, which upon activation with an alkoxide,[20] furnished the reactive nucleophilic CHF_2 element (Scheme 1 – *path f*).

We envisioned a modular and general methodology dealing with the direct transfer of various nucleophilic CHXY units to Weinreb amides[21] *en route* to geminal dihalogenated ketones. The nature of the halogens to be incorporated is simply selected depending on the operator's needings, being the wide commercially availability of the precursors dihalomethanes an additional advantage for the implementation of the strategy. Evidently, the formal dihalogenated homologating agents are lithium carbenoids (LiCHXY)[22] which – in contrast to fluorinated counterparts[23] – manifest a significant chemical integrity, fully preserved during the nucleophilic substitution, thus enabling the effective use of these organometallics (Scheme 1 – *path g*).

Results and Discussion

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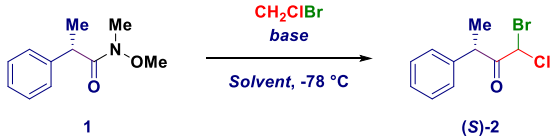
The inherent different reactivity imparted by the two distinct halogens to the α-position of a ketone [*e.g.* (C–Br bond dissociation energy = 72 kcal/mol *vs.* C–Cl bond dissociation energy = 85 kcal/mol],[24] motivated us to primary address their synthesis. As the model reaction, the transfer of LiCHBrCl to the optically active Weinreb amide **1** (> 99:1 *er*) was selected with the aim to evaluate not only the delivery of the carbenoid, but also the preservation of the chiral information contained (Table 1).[25] The constitutional acidity of the methylenic protons of $BrCH_2Cl$ (1.6 equiv) ensured the smooth formation of the transfer agent *via* treatment with the common LDA base (1.5 equiv) under Barbier-type conditions at -78 °C in THF. Bromochloro-ketone (*S*)-**2** was prepared in a good 59% isolated yield (76% ^{1}H-NMR conversion) and 95:5 *er* (entry 1). Presumably, the detectable loss of material during the chromatographic purification was caused by decomposition phenomena triggered by silica gel. Because under identical conditions no significant yield improvement was achieved when chromatography was conducted on Alox (Brockmann degree III)[25a] (entry 2), we hypothesized that forcing the reaction towards completion could result in higher chemical yield. Under analogous stoichiometric conditions, bases such as LTMP, LHDMS, $LiNEt_2$ and LiNCy(*i*-Pr) afforded (*S*)-**2** in comparable conversion and *er*, thus suggesting that the nature of the base was not critical for maximizing the yield (entries 3-6). Taking into account that changing the solvent (diethyl ether, toluene, 2-MeTHF[26] – entries 7-9) was detrimental and confirmed the high performance of the good coordinating solvent THF, we tuned the stoichiometry and, effectively found it pivotal for the transformation. As expected, the use of a small excess of carbenoid lowered the efficiency (entry 10), while the progressive increase of the nucleophile loading enabled to generate (*S*)-**2** in an excellent 90% yield (95% conversion, entry 12) and 99:1 *er* after a fast filtration on a plug of silica gel. Some additional points merit mention: a) keeping the temperature at -78 °C was crucial for preserving the optical information (entry 13, run at -60 °C);[27] b) no deprotonating (and racemizing) effect was displayed by the Li base on the sensitive α-methyl-substituted Weinreb amide; c) although in principle, the reaction could be run with preformed LiCHBrCl (entry 14), the employment of Barbier-type conditions guarantees higher performances in terms of both yield and *er* (entry 12). This is a particularly significant aspect demonstrating the better integrity of dihalocarbenoids in sharp contrast with the pronounced chemical instability of monohalomethyllithiums (requiring mandatory Barbier-type conditions).[28] Additionally, it should be mentioned that also a mixed Mg/Li base (Knochel-Hauser type)[29] can be effective for the process, though the tamed magnesium carbenoid (ClMgCHBrCl-LiCl)[30] did not ensure high conversion (entry 15).

Table 1. Reaction optimization.

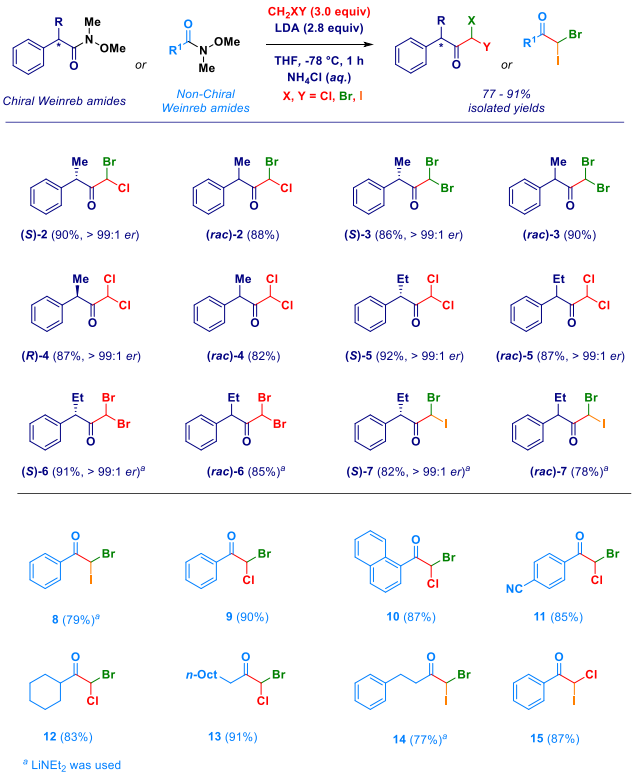


Entry	Base	LiCHBrCl (equiv)	Conversion [a]	Yield of (*S*)-**2** (%)[b]	*er* of (*S*)-**2**
1	LDA	1.5	76	59	95:5
2[c]	LDA	1.5	75	60	95:5
3	LTMP	1.5	72	56	94:6
4	LHDMS	1.5	66	51	97:3
5	$LiNEt_2$	1.5	74	58	95:5
6	LiNCy*i*Pr	1.5	70	55	98:2
7[d]	LDA	1.5	58	53	96:4
8[e]	LDA	1.5	49	36	95:5
9[f]	LDA	1.5	52	37	92:8
10	LDA	1.2	64	50	98:2
11	LDA	2.3	87	79	98:2
12	LDA	2.8	95	90	99:1
13[g]	LDA	2.8	89	83	98:2
14[h]	LDA	2.8	90	81	97:3
15[i]	MTMP	2.8	67	51	98:2

Unless otherwise stated the carbenoid was formed in Barbier-type conditions using a small excess of $BrCH_2Cl$ (*ca.* 10%) with respect to the base.[31] Upon preformation of the base, it was added to the mixture of Weinreb amide and $BrCH_2Cl$ through a syringe pump (0.2 mL/min rate).[32]
[a] The ratio has been determined by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [b] Isolated yield after purification. [c] Chromatography on Alox (Brockmann grade 3). [d] Run in Et_2O. [e] Run in toluene. [f] Run in 2-MeTHF. [g] Temperature – 60 °C. [h] LiCHBrCl was firstly prepared and after 1 min was added to **1** (*i.e.* non-Barbier conditions). [i] TMPMgCl·LiCl.

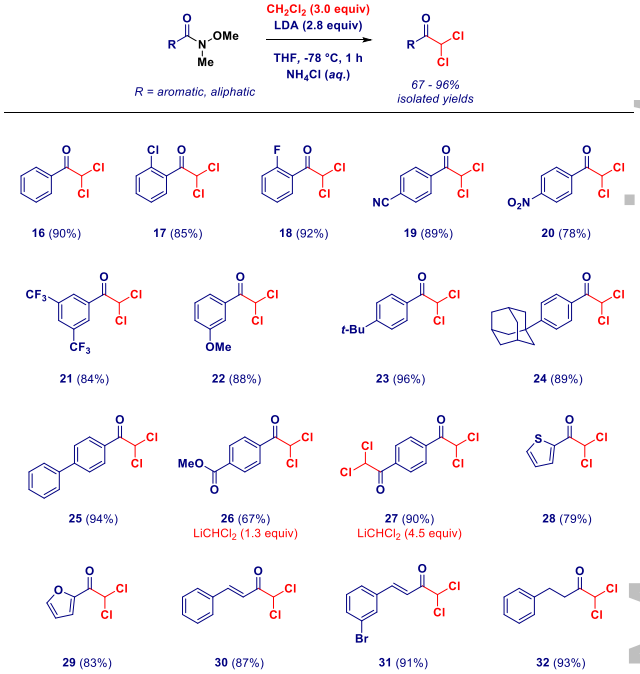
With the optimized condition in hand, we then studied the scope of the homologative dihalomethylation reaction (Scheme 2). The effectiveness of the procedure for preparing mixed *gem*-dihaloketones was deducted not only in the case of chiral and racemic bromochloro analogues, but also in the cases of dibromo (**3**, **6**), dichloro (**4**, **5**) derivatives. It is interesting to note that the more sterically hindered bromoiodomethane could be efficiently

deprotonated only with with $LiNEt_2$, thus giving the mixed bromoiodo carbenoid for preparing the unprecedented chiral (and racemic) ketone **7** in high yield and excellent enantiopurity. The methodology was flexible for preparing diversely functionalized mixed dihaloketones from both aromatic and aliphatic Weinreb amides such as the bromoiodo (**8**, **14**), bromochloro (**9**-**13**) and iodochloro (**15**)[33] derivatives. It is worth noting that no concomitant attack of LiCHBrCl on the sensitive aromatic nitrile was observed.



Scheme 2. Synthesis of mixed chiral (and racemic) *gem*-dihaloketones.

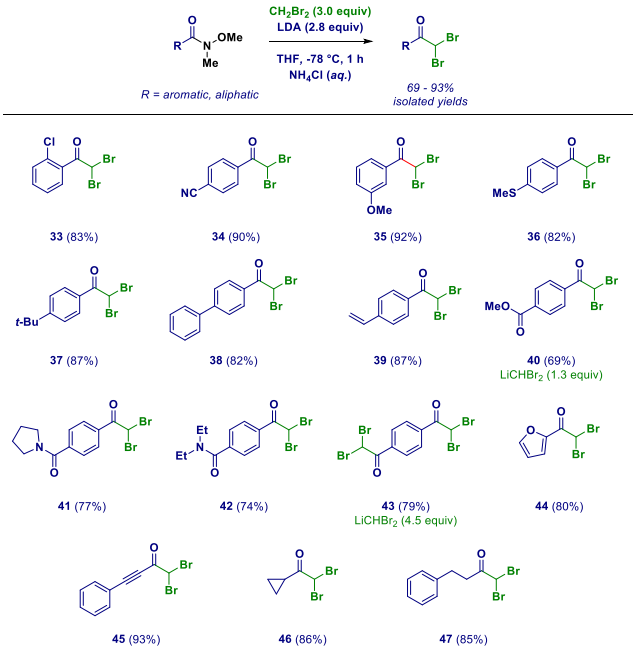
To gain full advantage of the protocol, the synthesis of dichloroketones was then studied (Scheme 3). Uniformly high yields and excellent chemocontrol were noticed under analogous deprotonating conditions of CH_2Cl_2. Aromatic Weinreb amides smoothly underwent the dichloromethylation procedure in the presence of a plethora of decorating elements on the nuclei. Halogens-containing motifs (**17**-**18**, **21**) were tolerated, as well as, the more challenging nitrile (**19**) and nitro (**20**) groups. The presence of motifs of different electronic behaviour was not detrimental as deducted in the cases of methoxy (**22**), *t*-Bu (**23**), 1-adamantyl (**24**) and phenyl (**25**). Pleasingly by controlling the stoichiometry (1.3 equiv), a single dichloromethylation could be run on an ester-featuring Weinreb amide, furnishing ketone **26** in which the alkoxycarbonyl group was untouched. Oppositely, an excess of carbenoid loading (4.5 equiv) permitted the double functionalization of a 1,4-bis Weinreb amide, giving the tetrachlorinated ketone **27**. Heteroaromatic [2-thienyl (**28**) and 2-furanyl (**29**)], as well as, α,β-unsaturated (**30**-**31**) or fully saturated systems (**32**) could also be efficiently prepared under full chemocontrol (*i.e.* no modification of olefin in **30**-**31**,[34] integrity of C_{Ar}-Br bond in **31**).



Scheme 3. Chemoselective preparation of *gem* dichloroketones.

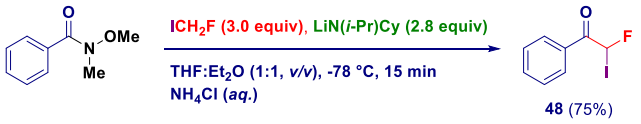
The synthesis of *gem*-dibromoketones further expanded the potentiality of the method, confirming the genuine chemoselectivity pattern previously discussed (Scheme 4). A series of aromatic functionalized analogues were uniformly prepared in high yield, regardless the modulating effect displayed by the substituents on the ring (**33**). In this sense, we appreciated once more the high chemoselective profile of the acylic substitution on a nitrile bearing material (**34**), as well as, on ether, thioether, alkyl or aryl presenting species (**35**-**38**). The terminal vinyl motif – potentially representing a cyclopropyl precursor with carbenoid reagents[35] – remained unaffected during the sequence (**39**). With much of our delight the dibromomethylation reaction proceeded with excellent chemocontrol not only in the case of an ester-containing substrate (**40**) but, more intriguingly also in the cases of carboxamide-substituted frameworks. As such, the nucleophilic attack of $LiCHBr_2$ could be

selectively directed on the Weinreb amide moiety, leaving unaffected the *per se* reactive pyrrolidinyl- (**41**) and diethyl- (**42**) amide residues. Analogously to dichloromethylation, in the presence of an excess of reagent, both Weinreb amide sites were functionalized, giving the symmetrical tetrabromoketone **43**. The versatility of the methodology was further showcased by the preparation of a heteroaromatic (2-furyl, **44**), a alkyne-containing (**45**) and aliphatic [cyclopropyl (**46**), ω-phenylpropyl (**47**) dibromoketones.



Scheme 4. Chemoselective preparation of *gem*-dibromoketones.

Our strategy was then employed for preparing a fluoro-iodoketone, a particularly challenging mixed *gem*-dihalo ketone for which available synthetic procedures are rather limited.[15] To this end, we conceived the employment of fluoro-iodomethyllithium firstly described by our group in 2019.[36] During the experiment design, we wondered if LiCHFI could efficiently react with the Weinreb amide as – in the case of carbon electrophiles – selectivity for diaryl ketones and activated imines was noticed (also in the presence of highly reactive fragments such as aldehyde or alkyl-arly ketones).[36b] Gladly, upon deprotonating the commercially available and easily manipulable ICH_2F (bp 52 °C)[37] with LiNCy(*i*-Pr), ketone **48** was formed in 75% isolated yield.



Scheme 5. Direct synthesis of a fluoroiodoketone with LiCHFI.

Conclusion

In summa, a modular, high-yielding strategy for the synthesis of α,α-dihaloketones through the acylic nucleophilic substitution on Weinreb amides with dihalomethyllithium carbenoids has been reported. The intrinsic acidity of the methylenic protons of various dihalomethanes (CH_2Cl_2, CH_2Br_2, $BrCH_2Cl$, ICH_2Cl, ICH_2Br, ICH_2F) enables the selective lithium-amide triggered deprotonation, thus furnishing the competent nucleophiles. The selectivity of the deprotonating operation guarantees the precise generation of the corresponding LiCHXY which can be delivered to the recipient acylating agent with the *exact* degree of halogenation demanded. Despite the use of strong alkaline conditions no racemization phenomena are observed when Weinreb amides embodying stereochemical information are employed. The procedure manifests a remarkable chemoselectivity profile as documented by examples involving the employment of multi-decorated analogues. Thus, sensitive functionalities (*e.g.* esters, nitriles, olefins, alkynes, halogen-containing motifs, amides) can be accommodated across the reactive fragment without interfering with the attack of the nucleophiles.

Experimental Section

General procedure for the dihalomethylation of Weinreb amides to *gem*-dihaloketones.

The Weinreb amide (1.0 equiv) was dissolved in dry THF, followed by the addition of the competent dihalomethane (3.0 equiv), under Argon and cooled down to -78 °C. To this solution, the preformed LDA [generated from *N*,*N*-di-*i*-propylamine and MeLi-LiBr at 0 °C in THF, 2.8 equiv] was added *via* syringe pump (0.2 mL/min rate) and then, the resulting mixture was stirred for 1 h. Subsequently, it was quenched with aqueous saturated NH_4Cl solution. The resulting organic phase was extracted 3 times with Et_2O, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude compounds were purified on a short plug of silica gel.

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