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A Straightforward Homologation of Carbon Dioxide with Magnesium Carbenoids en Route to α-Halocarboxylic Acids

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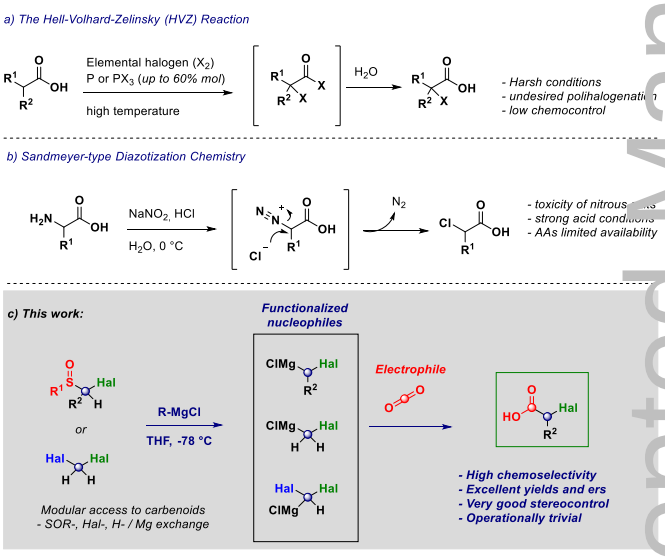
Abstract. The homologation of carbon dioxide with stable, (enantiopure) magnesium carbenoids constitutes a valuable method for preparing α-halo acid derivatives. The tactic features a high level of chemocontrol, thus enabling the synthesis of variously functionalized analogues. The flexibility to generate magnesium carbenoids through sulfoxide-, halogen- or proton- Mg exchange accounts for the wide scope of the reaction.

Keywords: Grignard reaction; Carbenoids; Carbon dioxide fixation; Carboxylic acids; Halogenation

The presence of α-halogen substituents to a C=O bond finely modulates the reactivity profile, thus making the resulting scaffolds valuable entities.[1] In this scenario, α-halo carboxylic derivatives occupy a prominent position also in view of their relevance in biology[2] and agrochemistry.[3] The Hell-Volhard-Zelinsky (HVZ) reaction represented the classical approach to these compounds (Scheme 1a):[4] the treatment of a carboxylic acid with elemental halogen in the presence of a quasi-stoichiometric phosphorous catalyst at high temperatures furnishes the targeted adducts. However, a series of drawbacks severely limits its applicability: 1) the harsh reaction conditions (*i.e.* up to 150 °C and long times) may trigger undesired elimination processes to α,β-unsaturated carboxylic acids;[5] 2) free radical processes come into play, furnishing mixtures of monohalo- and polyhalo-acids, thus affecting regio- and chemoselective aspects;[5b, 6] 3) attempts to improve the above mentioned issues (using of chlorine gas,[7] transformations into acylphosphonates followed by SO_2Cl_2 hydrolytic treatment[8]) are not suitable for large-scale processes. Because of the high relevance of chiral acids in synthesis,[1a] the obtainment of the corresponding α-haloacids is intriguing and often relies on multi-steps, low efficient procedures based on enzymatic methods,[9] use of silyl enol ethers in the presence of Lewis chiral acids[10] or, the use of auxiliaries.[11] Although under significant chemocontrol, the diazotization (*i.e.* Sandmeyer chemistry) requires the use of the highly toxic nitrous acid salts, thus posing important hazard limitations (Scheme 1b).[12]



Scheme 1. General context of the presented work.

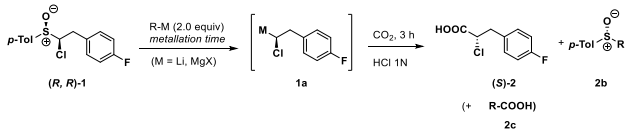
In line with research currently undergoing in our group on the employment of α-functionalized organometallic reagents,[13] we conceived a conceptually simple homologative approach based on the addition to carbon dioxide (CO_2, electrophile) of a nucleophilic halomethyl metal derivative (MCHRX,[14] Scheme 1c). Both these reactive elements present unique and advantageous features in terms of efficiency: 1) Carbon dioxide is a non-toxic, renewable C1 building block abundant in the atmosphere, constituting nowadays a precious synthon for

organic transformations;[15] 2) The good nucleophilic behaviour of MCHRX reagents allows to overcome the (catalytic) activation of the electrophile,[15c,16] as also suggested by the heterocumulene nature of this electrophile;[17] 3) Paved on our own previous studies, MCHRX reagents enable the formal insertion of CHRX fragments presenting the exact degree of functionalization thus, circumventing *de facto* selectivity issues (polyhalogenation).[13a, 18]

Herein, we present a straightforward preparation of α-halo carboxylic acids through an expeditious addition of magnesium carbenoids to CO_2. Once the (functionalized) carbenoids are properly generated, the subsequent simple bubbling of CO_2 ensures their smooth carboxylation which upon trivial acid-base treatment affords the targeted compounds in excellent yields.

We selected the diasteropure, easily accessible sulfoxide **(*R*,*R*)-1** (95:5 *dr*, > 99:1 *er*) as the model substrate for evaluating the carboxylation of the corresponding Hoffmann-type enantioenriched carbenoid.[19] The smooth sulfoxide-metal exchange,[20] indicative for the successful genesis of this species, was unambiguously evidenced by the concomitant formation of the addition`s product of the organometallic reagent to the sulfoxide (**2b**). The use of a lithium carbenoid through the addition of MeLi-LiBr to a carbon dioxide saturated solution of **1** (entry 1) under Barbier-type conditions resulted in the formation of simple acetic acid (**2c**). Evidently, these conditions interfered with the proper generation of the carbenoid, thus resulting in competing attack. Similarly, the renewed instability of Li carbenoids[14, 21] accounted for complete lack of reactivity when carbon dioxide was added after 10 min (entry 2). The switching to a more stable – but less nucleophilic – Mg carbenoid[22] was pivotal for the success of the transformation. Accordingly, *i*-PrMgCl, *i*-PrMgBr and the turbo Grignard (*i*-PrMgCl-LiCl)[23] gave promising, comparable results in terms of yield and enantiopurity (entries 3-5). Further improvement was achieved with cyclohexylMgCl (CyMgCl): Upon a metallation time of 60 min, followed by CO_2 bubbling, the enantiopure α-chloroacid (***S***)-**2** was obtained in an excellent 90% yield and 91:9 *er* (entry 6). Shortening the metallation time to 30 min, resulted in non-complete carbenoid formation – albeit in negligible effect on stereofidelity (entry 7). Operationally, employing CyMgCl appears very convenient because of the extremely easy removal of cyclohexyl *p*-tolylsulfoxide (**2b**), thus limiting the work-up to a trivial acid-basic work up procedure. Two additional points merit mention: 1) THF performed better than Et_2O in terms of both yield and *er* (entry 8); 2) although reactivity was observed at -60 °C (entry 9), the significant loss of stereochemical information suggested that -78 °C is the optimal one. Importantly, during the reaction with CO_2, inversion of configuration at the carbon atom was noticed in analogy with previous reports by Hoffmann dealing with alkylation of analogous reagents.[24]

Table 1. Reaction optimization.[a)]



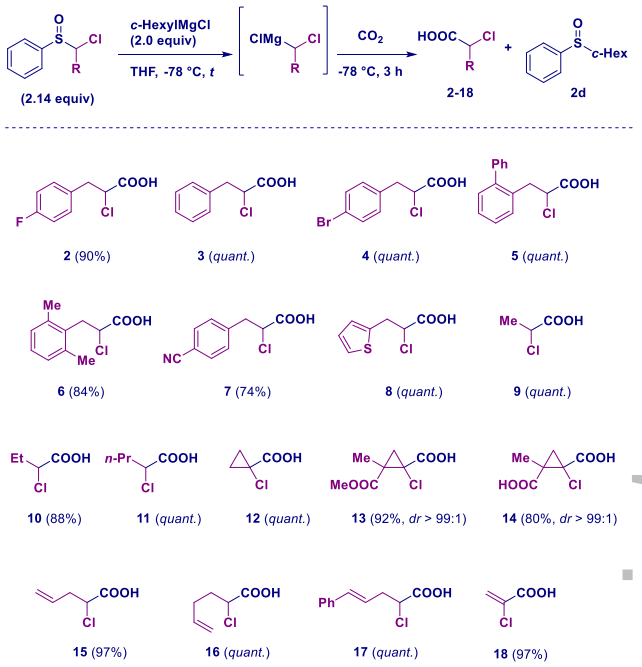
Entry [a)]	R-M	Metalation time (min)	**(*S*)-2** / **2b** / **2c** ratio (%)[b)]	Yield **(*S*)-2** (%)[c)]	*er*[d)] **2**
1[e)]	MeLi-LiBr	-	0 : 10 : 90	0	-
2	MeLi-LiBr	10	0 : 100 : 0	0	-
3	*i*-PrMgCl	60	27 : 73 : 0	80	91:9
4	*i*-PrMgBr	60	28 : 72 : 0	85	91:9
5	*i*-PrMgCl-LiCl	60	29 : 71 : 0	88	91:9
6	CyMgCl	60	30 : 70 : 0	90	91:9
7	CyMgCl	30	22 : 40 : 38[f)]	45	91:9
8[g)]	CyMgCl	60	20 : 80 : 0	60	87:13
9[h)]	CyMgCl	60	22 : 80 : 0	63	93:15

[a)] Otherwise stated, the following conditions were used: sulfoxide **(*R*,*R*)-1** (2.14 equiv, 95:5 *dr*, > 99 *er*), THF, -78 °C. [b)] The ratio was deducted by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as internal standard. [c)] Isolated yields after acid-basic work up (see SI). [d)] *er* was determined by chiral HPLC analysis on the methyl ester derivative **2a** (see ESI). [e)] Barbier-type conditions were used. [f)] Unreacted sulfoxide (***R*,*R*)-1** was recovered in 50% yield. [g)] Et_2O was used as solvent. [h)] Reaction run at -60 °C. Compound (***R*,*R*)-1** (CCDC 1879521).

With the optimized condition in hand, we then studied the scope of the reaction (Scheme 2). Readily accessible benzyl-type sulfoxides served as excellent placeholders for the corresponding Mg carbenoids by simple treatment with CyMgCl for the appropriate metallation time (see SI) prior to CO_2 bubbling. The acids (**2**-**18**) were obtained together with cyclohexyl phenyl sulfoxide **2d**, which could be separated through a trivial acid-basic work-up. The protocol showed a remarkable chemoselectivity, as noticed where potentially exchangeable halides could interfere (**4**). The steric hindrance on aromatic sulfoxides did not

constitute a limitation (*e.g.* 2-phenyl, 2,6-dimethyl derivatives **5**, **6**), thus delivering the desired α-chloroacids in excellent yields. The incorporation of an additional electrophilic functionality as nitrile amenable for further manipulation (**7**, *vide infra*) – known to be sensitive to Grignard reagents – was perfectly tolerated, as well as, the heterocyclic thienyl ring (**8**). Further evidence of the versatility of the protocol was deducted by the straightforward, modular access to a series of homologous α-chloro acids [*e.g.* 2-chloropropionic (**9**), 2-chlorobutanoic (**10**) and 2-chloropentanoic (**11**)] respectively. Our methodology offers clear advantages in terms of experimental simplicity and efficiency compared to a previous synthesis of **9** paved on a magnesium enolate formed from a α-sulfinyl-α-chloro acid.[25] Rigidifying the sulfoxide core enabled the preparation of cyclopropyl-type magnesium carbenoids[26] which gave the corresponding haloacids **12**-**14** in uniformly high to excellent yields, again with better efficiency than reported strategies: for example, acid **12** was prepared in 14% with a chlorination protocol.[27] Furthermore: 1) substitution across the cyclopropyl ring was perfectly tolerated; 2) the concomitant presence of a reactive ester (**13**) and an acid (**14**) were fully compatible with the reaction conditions. In this regard, starting from the diastereopure tetrasubstituted α-chlorocyclopropylsulfoxides, acids **13**, **14** were obtained with remarkable diastereoretention and chemocontrol. The presence of unsaturated elements was not affecting the technique, regardless their relative position and the substitution pattern across the olefin (**15**-**17**). Notably, the carboxylation of the Mg sp^2-carbenoid α-chloroalkylidene furnished 2-chloroacrylic acid **18** in 97% yield.

The halogen-magnesium exchange was employed for accessing carbenoids precursors of α-haloacetic acid derivatives through a single synthetic operation conducted on commercially available 1,1-dihalomethanes (Scheme 3a).[28]



Scheme 2. Scope of the sequential sulfoxide-Mg exchange / carboxylation. Isolated yields after acid-basic work up are reported.

Indeed, the use of magnesium carbenoids (XCH_2Mg) was pivotal for overcoming the limitation pointed out in early seminal studies by Köbrich who observed the formation of **19** in only 4% yield with lithium carbenoids.[29] We could observe also the limited suitability of a Magnus's-type stabilized lithium carbenoid[30] (**Li-22**) which provided the chloro acid **19** in significant lower yield (63%, Scheme 3b) compared to the Mg carbenoid. By simply selecting the carbenoid precursor, bromoacetic acid **20** and iodoacetic acid **21** were obtained from bromoiodomethane and diiodomethane, respectively.[31] By adopting a deprotonation strategy on dihalomethanes, the corresponding dihalomagnesium carbenoids were easily prepared by using the Knochel-Hauser base (TMPMgCl-LiCl).[32] The technique was general in scope, thus enabling the preparation of α,α-dihaloacids:[13h] dichloro- and dibromo- acetic acid (**23**-**24**) could be easily accessed, as well as, the mixed analogues bromochloro **25** and chloroiodo **26** (Scheme 3c). This is quite remarkable since a given dihalomethane is perfectly flexible for generating *three* different types of carbenoids, by uniquely selecting the reaction conditions.

The stability of magnesium carbenoids suggested us to design a carboxylation process involving species featuring multiple reactivity sites. In this context, we identified the sulfoxide **27** decorated with a cyclic hydroxyl-allylic moiety as a challenging carbenoid precursor.

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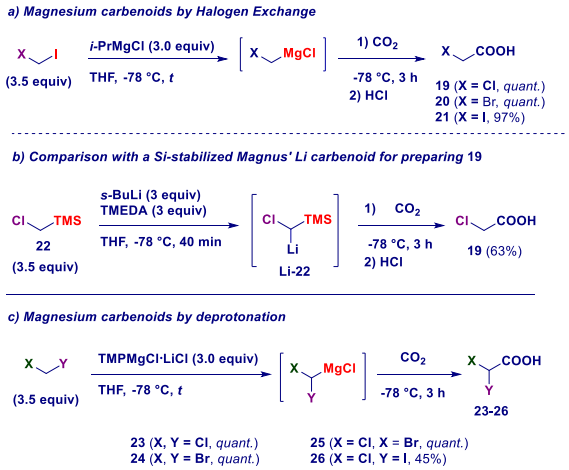
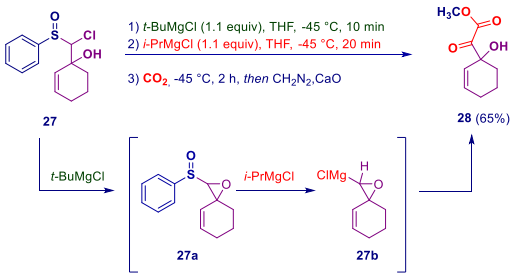


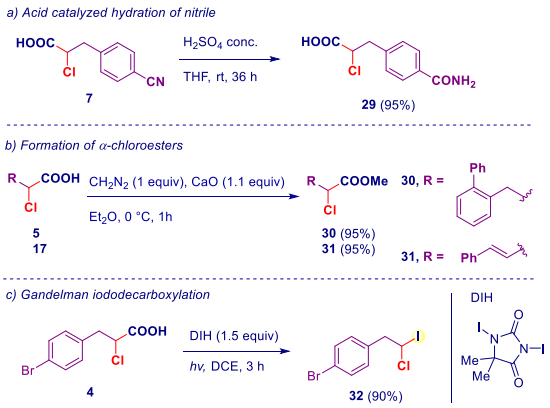
Scheme 3. Synthesis of α-halo and α,α-dihaloacids *via* halogen- or proton-Mg exchange. Isolated yields after acid-basic work up are reported.

Upon deprotonation with the sterically demanding *t*-BuMgCl, it is conceivable the formation of an epoxy-sulfoxide (**27a**)[33] which underwent smooth exchange with *i*-PrMgCl, thus furnishing the unknown Grignard-epoxide **27b**. In agreement with our own previous studies on the Meinwald-type epoxides-carbonyls rearrangement,[34] it would subsequently undergo carboxylation and hydration to give the corresponding methyl ester **28** after treatment with diazomethane.[35] Its structure was unambiguously confirmed by detailed NMR investigations and notably, the high chemical shift of the tertiary alcoholic functionality (13.05 ppm) observed in ^{1}H-NMR was diagnostic for a H-bond between a hydroxyl group and the vicinal ketone group (Scheme 4).



Scheme 4. Carboxylation of a multi-functionalized Mg carbenoid. Isolated yields after chromatography purification are reported.

With the aim to gain full insight into the potential of the new synthesized building blocks, we realized selective manipulations on their skeleton. The acidic hydrolysis of the cyano derivative **7** furnished the halo-acid **29** presenting a primary amidic functionality on the aromatic ring (Scheme 5a). Upon CaO-mediated diazotization methyl esters **30**, **31** were smoothly obtained,[35] thus enabling the synthesis of these synthetic valuable motifs in just two sequential, high yielding steps from trivial precursors (Scheme 5b). Gratifyingly, by applying the elegant Gandelman iododecarboxylation methodology we were able to selectively obtain the chloroiodo derivative **32** in high yield (Scheme 5c).[36] Such a three-different halogen scaffold would represent the formal alkylation product of a MCHICl carbenoid with a benzyl halide. However, according to previous studies by Hoffmann[19b] this highly unstable species (-105 °C) is not particularly suitable for alkylation-type reaction, thus making highly convenient the development of this route.



Scheme 5. Manipulations of α-haloacids. Isolated yields after chromatography purification are reported.

In summary, we have developed a straightforward synthesis of α-halo or α,α-dihalo carboxylic acids *via* the addition of nucleophilic (functionalized) magnesium carbenoids to the environmentally benign electrophilic carbon dioxide. The significant stability of magnesium carbenoids – compared to lithium analogues – together with their easy generation *via* sulfoxide-Mg, halogen-Mg and proton-Mg exchange allows to access with remarkable chemocontrol a wide series of halo acid derivatives in a single synthetic operation. That is, once the nucleophilic carbenoid synthon featuring the desired grade of functionalization (*i.e.* halogenation) is generated, it is rapidly transferred to CO_2, thus circumventing limitations affecting previously known methodologies.

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Formal Coupling en Route to α-Halocarboxylic Acids: A Straightforward Homologation of Carbon Dioxide with Magnesium Carbenoids

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